Department of Veterans Affairs

ANNUAL REPORT TO CONGRESS

Federally Sponsored Research on Gulf War Veterans' Illnesses for 2001

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Research Working Group of Military and Veterans Health Coordinating Board

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EXECUTIVE SUMMARY

I. INTRODUCTION

The Secretary of Veterans Affairs is required to submit to the Senate and House Veterans' Affairs Committees an annual report on the results, status, and priorities of research activities related to the health consequences of military service in the Gulf War. The Research Working Group (RWG) of the Military and Veterans Health Coordinating Board (MVHCB) prepared this document, the 2001 *Annual Report to Congress*, which is the eighth report on research and research activities. (PGVCB, 1995a; 1996a; 1997; 1998a; 1999a; 2001; MVHCB, 2001a). *

This Annual Report is divided into six sections. Section I is an introduction. Section II highlights and summarizes research progress since the last Annual Report. Section III is an analysis of the Federal Government's portfolio of research on Gulf War veterans' illnesses. Section IV highlights significant new research projects and initiatives since the last Annual Report. Section V discusses the management of Federal Gulf War veterans' illnesses research programs, including research oversight, peer review, and coordination. Section VI discusses priorities established in 1995, 1996, and 1998 for future research, and highlights the progress to date.

II. RESEARCH RESULTS IN 2001

In the past year, several research studies have yielded results that provide new and expanded information on the health problems of Gulf War veterans. Section II provides brief summaries of research projects for which results were published from January 2001 to December 2001. The RWG tracks all Federally funded research projects related to Gulf War veterans' illnesses. As in previous Annual Reports, research studies summarized in Section II are grouped according to nine focus areas: symptoms and general health status, brain and nervous system function, reproductive health, mortality, treatment, prevention, depleted uranium, pyridostigmine bromide, and interactions of exposures.

1. Symptoms and General Health Status:

Nine large studies published in 2001 focused on symptoms and general health. (Cherry, et al., 2001a; Cherry, et al., 2001b; Bourdette, et al., 2001; Spencer, et al., 2001; Chalder, et al., 2001; Reid, et al., 2001; Proctor, et al., 2001a; Proctor, et al., 2001b; Blood and Aboumrad, 2001) These publications included the results of studies conducted at four Federally-funded research centers in Portland, Boston, San Diego, and London, UK. Each of the studies included hundreds to thousands of individuals. Four of these studies were population-based, which means that the results of these studies may have implications for the overall population of 697,000 Gulf War veterans. (Cherry, et al., 2001a; Cherry, et al., 2001b; Chalder, et al., 2001; Reid, et al., 2001)

One of the most significant conclusions based on these recent studies and others is that Gulf War veterans do not suffer from a unique, previously unrecognized "syndrome." Five large, controlled studies have evaluated the health of thousands of Gulf War veterans and non-deployed veterans, involving the US Air Force; US Navy; US Army, Navy, and Air Force; and all three services from the United Kingdom, in two independent studies. (Fukuda, et al., 1998; Knoke, et al., 2000; Doebbeling, et al., 2000; Ismail, et al., 1999; Cherry, et al., 2001a) In each study, the patterns of symptoms reported by Gulf War veterans were similar to the patterns of symptoms reported by non-deployed veterans. In general, Gulf War veterans reported higher rates of the patterns of symptoms than the non-deployed veterans. However, non-deployed veterans occasionally reported higher rates of some of the patterns of symptoms. (Knoke, et al., 2000; Cherry, et al., 2001a)

2. Brain and Nervous System Function:

Six studies published in 2001 focused on brain and nervous system function, including posttraumatic stress disorder, major depression, and neuropsychological functioning. (Ford, et al., 2001; Erickson, et al., 2001; White, et al., 2001; Natelson, et al., 2001; Lange, et al., 2001; Schuff, et al., 2001) These publications included results of studies conducted at four Federally-funded research centers in Portland, Boston, New Orleans, and New Jersey. Five of these studies included hundreds to thousands of individuals. Five studies relied upon neurological and/or psychiatric evaluations, rather than relying solely on self-administered surveys. (Ford, et al., 2001; White, et al., 2001; Natelson, et al., 2001; Lange, et al., 2001; Schuff, et al., 2001)

*While this Annual Report was being written in March 2002, the Military and Veterans Health Coordinating Board was discontinued. However, inter-agency coordination among the collaborating departments is continuing.

Two of these six studies evaluated objective neuropsychological function. (White, et al., 2001; Lange, et al., 2001) Several populations of Gulf War veterans and non-deployed veterans have demonstrated consistent results on neuropsychological testing. Self-reported problems of memory and concentration have usually been more common among Gulf War veterans than among control subjects. However, on objective testing, performance was the same on most neuropsychological tests in Gulf War veterans and controls. In a small proportion of tests, such as attention or response speed, Gulf War veterans performed significantly more poorly than controls. After adjustment for PTSD, depression, or other psychological distress, the differences on the tests between the two groups often diminished or disappeared. (White, et al., 2001; Lange, et al., 2001; Anger, et al., 1999; Binder, et al., 1999; Storzbach, et al., 2000; Storzbach, et al., 2001; Vasterling, et al., 1997; Vasterling, et al., 1998)

3. Reproductive Health:

Three studies published in 2001 focused on reproductive health among Gulf War veterans and other military personnel. The objective of the first study was to compare the rates of self-reported birth defects in offspring of Gulf War veterans and non-deployed veterans. (Kang, et al., 2001)

The objective of the second study was to determine the feasibility of conducting active and passive surveillance for birth defects among infants of military beneficiaries. (Bush, et al., 2001) This was one of the first studies that was funded by a DoD Broad Agency Announcement related to research on Force Health Protection. Because of the success of this feasibility study, DoD endorsed a five-year project in 1998 to conduct DoD-wide birth defects surveillance among its health care beneficiaries. The objectives of the third study were to summarize the methodology of the DoD Birth Defects Registry, to describe the target population, and to highlight epidemiological studies that rely on Registry data. (Ryan, et al., 2001) The target population of the Registry consists of all live-born infants who are financially sponsored by DoD. The mother is identified as the active-duty member in 19% of DoD-sponsored births. Since 1998, the Registry has collected data on almost 90,000 births in military families each year, including about 7,000 births outside the U.S. About 60% of DoD-sponsored births have occurred at military facilities, and 40% of births have occurred at civilian medical centers. Consistent with other U.S. surveillance programs, the prevalence of all birth defects in 45 major malformation categories is calculated. Detailed analyses are underway, which link Registry data with military occupational exposure data, for example, data on anthrax vaccination (project DoD-99).

4. Mortality:

One study published in 2001 focused on mortality in Gulf War veterans. The objective of this study was to continue the follow-up of mortality of Gulf War veterans and non-deployed veterans through December 31, 1997. (Kang and Bullman, 2001) Overall mortality rates were similar in both groups (relative risk in Gulf War veterans of 0.95). There was a small, significant increase in motor vehicle fatalities in Gulf War veterans (1.19 times higher in males and 1.63 times higher in females). The risk of death from diseases (natural causes) was significantly lower in Gulf War veterans (relative risk of 0.83). This was mainly due to a significantly lower risk of death due to infectious diseases in Gulf War veterans (relative risk of 0.31), especially AIDS. No disease categories were significantly increased in Gulf War veterans. Among Gulf War veterans and non-deployed veterans, the overall mortality rates were 41% and 42% of the mortality rates in the general US population, respectively. This means that both groups of veterans were much healthier than persons of the same age in the general population. These results are very similar to results of a mortality study in British Gulf War veterans. (Macfarlane, et al. 2000) The US and UK mortality studies are continuing.

5. Treatment:

Two studies published in 2001 focused on treatment of illnesses in Gulf War veterans. The objectives of the first study were: to determine the frequency with which Gulf War veterans with health concerns met CDC criteria for "chronic multisymptom illness" (CMI); to determine which demographic variables or concurrent medical diagnoses were associated with CMI; and to design diagnostic tools to identify CMI, quantify severity of symptoms, and establish treatment strategies for symptomatic veterans. (Baker, et al., 2001)

The objective of the second study was to "survey general internal medicine clinicians and mental health clinicians to identify and contrast their beliefs about the causal attributions, clinical course, and treatment of medically unexplained physical symptoms in Gulf War veterans." (Richardson, et al., 2001) In November 1998, surveys were mailed to 135 providers in general internal medicine clinics (GIMC) and 400 providers in mental health clinics (MHC) at the Seattle and Portland VA Medical Centers. GIMCs were significantly more likely than MHCs to believe that illnesses in Gulf War veterans were the result of a "mental disorder," and that symptoms were due to stress or PTSD. In contrast, MHCs were significantly more likely to believe that these illnesses were the result of a "physical disorder," and that symptoms resulted from viruses or bacteria, exposure to toxins, chemical weapons, or a combination of toxins and stress. About 60% of both MHCs and GIMCs believed that treatment of illnesses in Gulf War veterans should incorporate an equal combination of biological and psychological interventions. The authors recommended "collaborative approaches that place clinicians with contrasting views of these conditions in regular proximity to one another for the purposes of building interdisciplinary rehabilitative interventions, sharing ideas, dispelling simplistic etiologic explanations, and attempting to optimize the consistency of information communicated to patients by all clinicians."

6. Prevention:

One study published in 2001 focused on prevention of illnesses in military personnel. The objectives of the study were to define the incidence of pneumonia caused by *Streptococcus pneumoniae* (the pneumococcus) more precisely in the U.S. military population; and to determine the efficacy of the vaccine in protecting healthy young adults. (McKeehan, et al., 2001) This large clinical trial of pneumococcal vaccine among 191,000 US military recruits has been undertaken as a result of recent outbreaks of pneumococcal disease and the emergence of increased antibiotic resistance. This was one of the first studies that was funded through a DoD Broad Agency Announcement related specifically to Force Health Protection.

7. Depleted Uranium:

Two studies published in 2001 focused on the effects of depleted uranium (DU) in Gulf War veterans. The objective of the first study was to demonstrate an assay method in urine, which could differentiate DU exposure from exposure to natural uranium. (Hodge, et al., 2001)

The objective of the second study was to determine the clinical health effects of DU through follow-up evaluation of exposed Gulf War veterans. (McDiarmid, et al., 2001b). In 1993, the Baltimore VA Medical Center began a study of Gulf War veterans who had been wounded in friendly fire incidents. In 1999, 50 veterans were examined. Of these, 21 had been examined in 1993-94 and 1997, and 29 were newly identified. In 1999, the 13 veterans with retained metal fragments continued to excrete elevated concentrations of urine uranium. In contrast, the 37 veterans without fragments excreted concentrations of uranium that were within the normal range. There were no differences found in kidney function tests between the high and low uranium groups. There were no significant differences between the high and low uranium groups on four neuropsychological tests. The authors concluded that subtle neuropsychological findings that were detected in 1997 have diminished. The 50 veterans who were examined in 1999 have fathered 35 children since the Gulf War, all without birth defects. The authors concluded that there were "relatively few abnormal clinical findings in this group" of 50 veterans. Medical surveillance of this cohort of DU-exposed veterans will continue indefinitely.

8. Pyridostigmine Bromide:

Three studies published in 2001 focused on the effects of pyridostigmine bromide (PB), two in laboratory animals and one in humans. The objective of one laboratory study was to investigate to what extent administration of PB could affect food motivation in Wistar-Hanover rats, as measured with a learned task. (van Haaren, et al., 2001a) The objective of the second laboratory study was to treat guinea pigs with PB to determine the effects on the blood-brain barrier, and on blood and brain cholinesterase levels. (Lallement, et al., 2001)

The objectives of the human study were "to quantify the type, intensity, and frequency of side effects of low-dose PB, and to examine

factors that predict the intensity and frequency of side effects." (Cook, et al., 2001) A double-blind, placebo-controlled design was used. 33 subjects received 30 mg PB every 8 hours for 13 doses (the standard military dose), and 34 subjects received 60 mg on the same schedule. Overall, side effects occurred infrequently and they were generally mild, even at the 60 mg dose. Even at the same dose level, however, some subjects reported more side effects than others, when taking both placebo and PB. An analysis was performed to determine the factors that were related to reported side effects during the PB week. The only factor that significantly predicted side effects during the PB week was side effects during the placebo week. The authors concluded: "PB is well tolerated by healthy young people, even when twice the recommended military dose is administered."

9. Interactions of Exposures:

Six animal studies published in 2001 focused on the health effects of interactions of exposures. These included four studies of the effects of pyridostigmine bromide (PB), in combination with foot shock stress, multiple vaccines, or other chemicals (DEET and permethrin). (Kant, et al., 2001; Griffiths, et al., 2001; van Haaren, et al., 2001b; and Abou-Donia, et al., 2001b) Two animal studies focused on the interactions of chemicals other than PB, in particular, DEET and permethrin. (Abou-Donia, et al., 2001a; Abdel-Rahman, et al., 2001)

Several studies have recently evaluated whether stress can increase blood-brain barrier (BBB) permeability, and can therefore enhance penetration of PB into the brain. These have included several species and strains of animals: 3 different strains of mice (Telang, et al., 1999; Chaney, et al., 1999; Grauer, et al., 2000); guinea pigs (Lallement, et al., 1998); and 3 strains of rats (Sinton, et al., 2000; Chaney, et al., 2000; Kant, et al., 2001). These studies have included several types of acute stressors: forced swimming stress (Telang, et al., 1999; Grauer, et al., 2000; Sinton, et al., 2000); heat stress (Lallement, et al., 1998; Sinton, et al., 2000); severe cold stress (Grauer, et al., 2000); restraint stress (Sinton, et al., 2000; Kant, et al., 2001); foot shock stress (Kant, et al., 2001); and chemical stress (coadministration of high doses of DEET) (Chaney, et al., 1999; Chaney, et al., 2000). All of these studies since 1998 have reached the conclusion that stress does not increase BBB permeability to PB, and that PB does not penetrate the brain, even at very high doses. In particular, one study concluded "to the extent that cross-species comparisons are valid" between humans and rodents, "the effects of stress on BBB permeability to PB are unlikely to explain the chronic CNS symptoms reported by some Gulf War veterans." (Sinton, et al., 2000)

III. RESEARCH FUNDING TRENDS

The Gulf War Veterans' Illnesses research portfolio currently includes 224 projects. It was last updated during the first quarter of Fiscal Year 2002 (through December 31, 2001). These 224 Federal research projects are sponsored by the Departments of Veterans Affairs (VA), Defense (DoD), or Health and Human Services (HHS). The scope of the Federal research portfolio is broad, from small pilot studies to large-scale epidemiology studies involving large populations and major research center programs. Currently, the Federal Government is projecting cumulative expenditures of $212.6 million for research from FY 1994 through FY 2002. As of September 30, 2001, 124 projects were completed (55% of total), and 100 projects were ongoing. The overall emphasis has been greatest in the focus areas of Symptoms and General Health Status, and Brain and Nervous System Function. The numbers of projects in each focus area are examined in more detail in Section III.

IV. NEW RESEARCH PROJECTS AND INITIATIVES

Besides new research findings appearing in the published scientific literature, there have been several important events since last year's *Annual Report to Congress* that deserve discussion. These include the awarding of new research projects and the development of new research initiatives. This section also updates important accomplishments in 2001 for key research projects and initiatives.

IV.A. NEW RESEARCH PROJECTS

IV.A.1. New Projects Funded by the 2000 DoD Broad Agency Announcements

In 1998, DoD established new funding for programmed research. The purpose of this program element funding is to address Gulf War

least one parent must be a DoD health care beneficiary, such as an active-duty member, active reservist, military retiree, or other dependent. The mother is identified as the active-duty member in 19% of DoD-sponsored births. The mother is a dependent of a military member or other beneficiary in 81% of births. Since 1998, about 60% of DoD-sponsored births have occurred at military facilities, and 40% of births have occurred at civilian medical centers. Consistent with other U.S. surveillance programs, the prevalence of all birth defects in 45 major malformation categories is calculated.

DoD's ability to access large, complete databases on all health care provided to its beneficiaries is a strength found in only a few managed-care programs. The ability of DoD to link its data on occupational exposures of its members is potentially an even greater asset. Detailed analyses are underway, which link Registry data with military occupational exposure data. The first study to use Registry data directly was recently initiated to explore possible long-term reproductive effects related to the anthrax vaccine (DoD-99). This study requires linking military service records, vaccination records, and birth defects data. Also, in the Millennium Cohort Study, survey-based and objective data will be collected prospectively on 140,000 service personnel, who will be followed over a 20-year time period (DoD-143). Data on deployments experienced by this cohort will be linked with Birth Defect Registry data.

3. Kang, H, Magee, C, Mahan, C, Lee, K, Murphy, F, Jackson, L, and Matanoski, G. Pregnancy outcomes among US Gulf War veterans: a population-based survey of 30,000 veterans. *Annals of Epidemiology* 2001 October; 11(7):504-511. **(VA-2)**

In 1995-98, VA performed a population-based survey, entitled the "National Health Survey of Gulf War Era Veterans and Their Families." (Kang, et al., 2000) The goal of the survey was to compare the health status of a sample of 15,000 Gulf War veterans with the health status of a sample of 15,000 non-deployed veterans. A total of 11,441 Gulf War veterans responded to the survey (75%), and 9,476 non-deployed veterans responded (65%). The questionnaire included various symptoms, medical diagnoses, and reproductive histories, including birth defects in children. The objective of this particular analysis was to compare the rates of self-reported birth defects in offspring of Gulf War veterans and non-deployed veterans. (Kang, et al., 2001) Two very large studies based on medical records have previously demonstrated that the rates of birth defects in the offspring of Gulf War veterans and non-deployed veterans were the same. (Cowan, et al., 1997; Araneta, et al., 2000)

6,043 of the 20,917 participants (29%) in the survey reported at least one pregnancy after June 30, 1991. Veterans who completed the survey were required to describe the birth defect in their own words. Study personnel reviewed the self-reported birth defects, interpreted the likely medical diagnoses that would match the veterans' descriptions, and classified the defects into a category of either "likely" or "unlikely" defects. The authors stated, "Some over-reporting of birth defects was expected because the survey did not predefine or provide examples of birth defects." 206 birth defects were categorized as "likely." The "unlikely" defects were estimated to be about 40% of the reported defects, and they were excluded from further analysis. Also, a subset of 146 "moderate to severe" defects was defined, that potentially required surgery or chronic medical supervision.

There were 2,236 live births reported by male Gulf War veterans, and 1,689 live births reported by male non-deployed veterans. There were 471 live births reported by female Gulf War veterans, and 577 live births reported by female non-deployed veterans. Male Gulf War veterans reported a significant increase of "likely" birth defects, compared to controls (OR=1.94; 95% C.I.=1.37-2.74). Female Gulf War veterans also reported a significant increase of "likely" birth defects, compared to controls (OR=2.97; 95% C.I.=1.47-5.99). The rates of "moderate to severe" defects were also significantly increased in male and female Gulf War veterans.

The authors cautioned that "The potential for participant bias in this study is of major concern since Gulf veterans may have been more disposed to participate if they had an adverse pregnancy outcome." Reporting bias by Gulf War veterans was also a serious concern in this study, because the increased rates of self-reported birth defects were consistent with increased rates of nearly every self-reported health outcome in the survey. For example, Gulf War veterans reported a significant increase in the frequencies of all 48 of the 48 symptoms on

the survey, compared to the controls. (Kang, et al., 2000) The authors concluded that the self-reported birth defects needed "to be confirmed by a review of medical records to rule out possible reporting bias." (Kang, et al., 2001) This review of medical records was underway, as of early 2002.

The final phase of the VA National Health Survey included a medical evaluation of 1000 Gulf War veterans and their families, and 1000 non-deployed veterans and their families. This phase included physical exams of veterans, spouses, and children, which were completed in 2001. Children received a pediatric examination, with particular attention to birth defects. Several adverse reproductive outcomes will be compared among Gulf War veterans and non-deployed veterans, including birth defects. The analysis of this final phase of the study should be completed in 2002.

D. Mortality

Kang, HK, and Bullman, TA. Mortality among US veterans of the Persian Gulf War: 7-year follow-up. *American Journal of Epidemiology* 2001 September 1; 154(5):399-405. **(VA-1)**

One study published in 2001 focused on mortality in Gulf War veterans. The objective of this study was to continue the follow-up of a mortality study of Gulf War veterans through December 31, 1997. (Kang and Bullman, 2001) The earlier study reported on the mortality rates of 621,902 Gulf War veterans and 746,248 non-deployed veterans, with follow-up through September 1993. (Kang and Bullman, 1996) There was small, but significant, increase in mortality due to all causes in Gulf War veterans (relative risk of 1.09). This excess was mainly due to unintentional injuries, mostly motor vehicle fatalities. The risk of unintentional injuries was 1.25 times higher in males and 1.83 times higher in females. The risk of death from diseases (natural causes) was lower in Gulf War veterans than non-deployed veterans (relative risk of 0.88).

This mortality study has been updated with the same cohorts, with follow-up through 1997. (Kang and Bullman, 2001) Mortality rates were adjusted for age, race, gender, marital status, branch of service, and active-duty vs. reserve/National Guard. Overall mortality rates were similar (relative risk in Gulf War veterans of 0.95). There continued to be a small, significant increase in motor vehicle fatalities in Gulf War veterans (1.19 times higher in males and 1.63 times higher in females). The risk of death from diseases (natural causes) continued to be significantly lower in Gulf War veterans (relative risk of 0.83). This was mainly due to a significantly lower risk of death due to infectious diseases in Gulf War veterans (relative risk of 0.31), especially AIDS. No disease categories were significantly increased in Gulf War veterans, such as cardiovascular diseases, cancer, or respiratory diseases.

Among Gulf War veterans, mortality risk was assessed relative to the possibility of exposure to nerve agents due to the demolition of munitions at Khamisiyah, Iraq in March 1991. 48,281 veterans were potentially exposed to very low levels of sarin, compared to 573,621 veterans who were probably not exposed. There was no increased risk in mortality due to all causes (relative risk of 1.01), all natural causes, or any other cause. Among Gulf War veterans and non-deployed veterans, the overall mortality rates were 41% and 42% of the age-adjusted mortality rates in the general U.S. population, respectively. The veteran groups also had significant decreases in most of the major disease categories. This means that both groups of veterans were much healthier than persons of the same age in the general U.S. population.

A mortality study of British Gulf War veterans demonstrated very similar results. (Macfarlane, et al., 2000) In both the US and the UK, Gulf War veterans have shown significantly higher mortality rates due to unintentional injuries compared to non-deployed veterans, mostly motor vehicle injuries. This is the only difference in mortality rates, to date. The mortality studies in the US and UK will continue indefinitely.

E. Treatment

Overview:

Two studies published in 2001 focused on treatment of illnesses in Gulf War veterans. The objectives of the first study were: to determine the frequency with which Gulf War veterans with health concerns met CDC criteria for "chronic multisymptom illness" (CMI); to determine which demographic variables or

concurrent medical diagnoses were associated with CMI; and to design diagnostic tools to identify CMI, quantify severity of symptoms, and establish treatment strategies for symptomatic veterans. (Baker, et al., 2001) The objective of the second study was to "survey general internal medicine clinicians and mental health clinicians to identify and contrast their beliefs about the causal attributions, clinical course, and treatment of medically unexplained physical symptoms in Gulf War veterans." (Richardson, et al., 2001)

Treatment-Individual Studies:

1. Baker, DG, McQuarrie, IG, Murray, MG, Lund, LM, Dashevsky, BA and Mendenhall, CL. Diagnostic status and treatment recommendations for Persian Gulf War veterans with multiple nonspecific symptoms. *Military Medicine* 2001 November; 166(11):972-981. **(VA-59)**

The objectives of this study were: to determine the frequency with which Gulf War veterans with health concerns met CDC criteria for "chronic multisymptom illness" (CMI); to determine which demographic variables or concurrent medical diagnoses were associated with CMI; and to design diagnostic tools to identify CMI, quantify severity of symptoms, and establish treatment strategies for symptomatic veterans. (Baker, et al., 2001) The authors adopted the working case definition for "chronic multisymptom illness" developed by the CDC in a study of Gulf War veterans in the Air Force. (Fukuda, et al., 1998) This included at least two of three categories of symptoms of fatigue, mood/cognition problems, and musculoskeletal problems, which lasted at least six months. Note, that Baker, et al., called these chronic symptoms "Gulf War illness" in their study; however, the term "chronic multisymptom illness" is used in this summary, because this CDC term has been used in several cohorts of Gulf War veterans. (Fukuda, et al., 1998; Nisenbaum, et al., 2000; Steele, 2000; Unwin, et al., 1999; Ismail, et al., 2000; Hotopf, et al., 2000; Chalder, et al, 2001; Proctor, et al., 2001b)

In 1998-2000, veterans with health concerns were recruited to participate in a treatment demonstration project at the Cincinnati and Cleveland VA Medical Centers. (Baker, et al., 2001) Data were summarized for the first 120 veterans who enrolled in the study. 22 veterans failed to complete follow-up assessments, often because of work conflict; and 9 veterans were excluded due to current, serious psychiatric conditions (5 ongoing substance abuse, and 4 bipolar disorder). 89 veterans completed physical examinations, laboratory tests, multiple structured psychiatric interviews, and the Medical Outcomes Study Short Form 36 (SF-36). Most of the 89 veterans were "relatively normal with respect to objective findings on physical exams, lab tests, and radiography." 41% of the 89 veterans received a medical, but not a psychiatric diagnosis; 52% received both a medical and psychiatric diagnosis; and 7% were healthy and did not receive a diagnosis. Therefore, more than 50% had a treatable depression or anxiety disorder. Veterans with depression and anxiety disorders were "indistinguishable," on the basis of the types of most severe symptoms, from veterans who received only medical diagnoses. Medical diagnoses in veterans were most often musculoskeletal disorders that are also frequent in the general population.

83% of the 89 veterans fulfilled CDC criteria for CMI. There were no significant differences on lab tests between the veterans with and without CMI, however there were several other significant differences between them. Those with CMI: were older; reported more combat exposure; scored higher on measures of depression, PTSD, and fibromyalgia; and reported poorer health-related quality of life on the SF-36. Almost all the veterans with depression (94%), PTSD (100%), and fibromyalgia (100%) fulfilled the CDC criteria for CMI. Veterans without CMI reported scores on the SF-36 that were equivalent to the national norms. Veterans with CMI scored significantly lower than the veterans without CMI on all 8 subscales of the SF-36. The SF-36 alone predicted the presence of one or more psychiatric diagnoses with a positive predictive value of 81.6. The predictions based on the SF-36 were correct for 84% of patients with psychiatric disorders, and for 82% of patients without psychiatric disorders. When the Hamilton D Scale for depression was added, the positive predictive value increased to 88.6.

The authors concluded that the great majority of veterans seeking care in the Gulf War Registry clinics in Cincinnati and Cleveland fulfilled the CDC criteria for CMI. Based on their diagnoses, veterans were offered an individualized program

including education, medical care, and psychiatric care, if indicated. Two models of care were compared: management by a primary care physician (Cleveland) and management by a multidisciplinary team that included a psychiatrist (Cincinnati). At both sites, clinicians recognized and accepted the veterans' feelings of uncertainty, anxiety, or alienation and responded with education. Both sites maintained close two-way contact with veterans through dedicated phone lines reaching a study coordinator at the Cleveland site and nurse case managers at the Cincinnati site. Similar to the model of care typical in chronic pain programs, clinicians at both sites treated medical and psychiatric disorders as they were diagnosed, but they placed primary emphasis on patient education with the goal of increased self-management of chronic symptoms.

2. Richardson, RD, Engel, CC, McFall, M, McKnight, K, Boehlein, JK, and Hunt, SC. Clinician attributions for symptoms and treatment of Gulf War-related health concerns. *Archives of Internal Medicine* 2001 May 28; 161(10):1289-1294. **(VA-58)**

The objective of this study was to "survey general internal medicine clinicians and mental health clinicians to identify and contrast their beliefs about the causal attributions, clinical course, and treatment of medically unexplained physical symptoms in Gulf War veterans." (Richardson, et al., 2001) When evaluating and treating individuals with medically unexplained physical symptoms, clinicians' beliefs might shape decisions regarding referral, diagnostic testing, and treatment. Some Gulf War veterans have developed chronic physical symptoms that have eluded diagnosis, and that have led to considerable diagnostic testing, extensive referrals, and uncertain treatment. The authors noted: "To date, no unique disease, toxic exposure, or pathophysiological mechanism has been established to explain these symptoms, and no definitive treatment has emerged."

In November 1998, surveys were mailed to 135 providers in general internal medicine clinics (GIMC) and 400 providers in mental health clinics (MHC). These providers worked at the Seattle and Portland VA Medical Centers. 77 (57%) of the 135 GIMCs and 214 (54%) of the 400 MHCs completed the survey. GIMCs were significantly more likely than MHCs to believe that illnesses in Gulf War veterans were the result of a "mental disorder," and that symptoms were due to stress or PTSD. In contrast, MHCs were significantly more likely to believe that these illnesses were the result of a "physical disorder," and that symptoms resulted from viruses or bacteria, exposure to toxins, chemical weapons, or a combination of toxins and stress. It is noteworthy, however, that almost 50% of both GIMCs and MHCs believed that these illnesses resulted from an equal combination of physical and mental disorders.

Both GIMCs and MHCs believed that these illnesses were not the result of compensation-seeking behavior. Both groups disagreed with the statement that these illnesses would go away with or without treatment. GIMCs were significantly more likely than MHCs to disagree with the statements that the illnesses were contagious, permanent, life-threatening, or in need of additional medical tests by a specialist. MHCs were more likely to endorse biological interventions to treat Gulf War veterans, whereas GIMCs were more likely to endorse psychological interventions. However, about 60% of both MHCs and GIMCs believed that treatment of illnesses in Gulf War veterans should incorporate an equal combination of biological and psychological interventions.

These results provided evidence that clinicians tended to invoke explanations outside the scope of their usual clinical knowledge, when dealing with the medical uncertainty associated with unexplained physical symptoms in Gulf War veterans. The authors concluded, "Clinicians' beliefs about the etiology and effective treatment of Gulf War illness vary and thus might contribute to the multiple referrals often reported by Gulf War veterans." They recommended "collaborative approaches that place clinicians with contrasting views of these conditions in regular proximity to one another for the purposes of building interdisciplinary rehabilitative interventions, sharing ideas, dispelling simplistic etiologic explanations, and attempting to optimize the consistency of information communicated to patients by all clinicians."

F. Prevention

McKeehan, JA, Ryan, MA, and Gray, GC. Pneumococcal vaccine to counter emerging infectious disease threat in the military. *Military Medicine* 2001 December; 166(12):1087-1090. **(DoD-96)**

One study published in 2001 focused on prevention of illnesses in military personnel. This was one of the first studies that was funded through a DoD Broad Agency Announcement related to Force Health Protection. Diseases caused by *Streptococcus pneumoniae* (the pneumococcus) include a broad spectrum of human disease, including invasive diseases such as pneumonia, meningitis, and sepsis. A vaccine to prevent pneumococcal diseases has been available in the US for about 25 years. Vaccination has been strongly recommended for the elderly and for very young children, yet its utility in young adults has not been well evaluated. In 1998, the Armed Forces Epidemiological Board recommended that the 23-valent vaccine be evaluated for use in high-risk military populations. So far, only one recruit training camp and some elite military groups (the Navy SEALs and Army Rangers) have chosen to provide this vaccine to their troops.

As a result of recent outbreaks of pneumococcal disease and the emergence of increased antibiotic resistance, a large clinical trial of pneumococcal vaccine among young adults enlisting in the US military has been undertaken by the Naval Health Research Center (NHRC) in San Diego. The objectives of the study are to define the incidence of pneumococcal disease more precisely in the U.S. military population and to determine the efficacy of the vaccine in protecting healthy young adults. (McKeehan, et al., 2001)

The NHRC, in collaboration with the CDC, the Mayo Clinic, Wyeth Lederle Vaccines, and a number of military commands, has initiated a large, double-blind placebo-controlled clinical trial of the 23-valent pneumococcal vaccine. A population of more than 191,000 recruits will be enrolled in the vaccine trial, actively followed during their 9 to 12 weeks of basic training, and passively followed for respiratory diseases for up to 15 months after training. Five recruit training centers are participating, including two Marine, one Navy and two Army centers. Recruits will be enrolled in the study from October 2000 to February 2002. All recruits will be followed closely for pneumonia during basic training. If they become ill, they will receive extensive medical evaluations and microbiological studies to determine the organism. For 15 months after basic training, hospitalizations at military medical facilities for pneumonia and any-cause acute respiratory disease will be identified and verified.

This vaccine trial is one of the largest double-blind placebo-controlled trials in DoD history. This research will provide important information to military policy makers, and it will have additional value for civilian public health professionals. This study may lead to new recommendations for the use of the vaccine in other populations of young adults, such as high school and college students or health care providers.

G. Depleted Uranium

Overview:

Two studies published in 2001 focused on the effects of depleted uranium in Gulf War veterans. The objective of the first study was to determine the clinical health effects of depleted uranium (DU) through follow-up evaluation of a cohort of Gulf War veterans who were exposed in friendly fire. (McDiarmid, et al., 2001b) The objective of the second study was to demonstrate an assay method that can differentiate DU exposure from exposure to natural uranium, in Gulf War veterans with or without retained metal fragments. (Hodge, et al., 2001)

Depleted Uranium-Individual Studies:

1. McDiarmid, MA, Squibb, K, Engelhardt, S, Oliver, M, Gucer, P, Wilson, PD, Kane, R, Kabat, M, Kaup, B, Anderson, L, Hoover, D, Brown, L, and Jacobson-Kram, D. Surveillance of depleted uranium exposed Gulf War veterans: health effects observed in an enlarged "friendly fire" cohort. *Journal of Occupational and Environmental Medicine* 2001b December; 43(12):991-1000. **(Funded by VA)**

In 1993, the Baltimore Veterans Affairs Medical Center began a prospective study of Gulf War veterans who had been wounded in friendly fire incidents, to quantify body burdens of uranium over time and to detect any adverse health effects from this exposure. (Hooper, et al., 1999; McDiarmid, et al., 2000; McDiarmid, et al., 2001a) The VA and DoD were concerned that embedded depleted uranium (DU) fragments could dissolve over time, potentially leading to toxic effects in the kidneys and other organs. In

1993-94, about half the group of 33 veterans demonstrated embedded metal fragments in soft tissues in various locations on skeletal surveys, and their urinary uranium concentrations were elevated. Other than the significant sequelae of traumatic injury, there was no association between uranium excretion and clinically detectable adverse health effects. (Hooper, et al., 1999) The primary finding of the second evaluation in 1997 was that elevated urinary uranium concentrations continued to be observed in veterans with retained metal fragments. There was also a significant association between high uranium levels and lowered performance on some, but not all, neuropsychological tests. (McDiarmid, et al., 2000)

The objective of this study was to determine the clinical health effects of depleted uranium in follow-up evaluation of a cohort of Gulf War veterans who were exposed in friendly fire. (McDiarmid, et al., 2001b) 50 veterans were examined in 1999. Of these, 21 had been examined in 1993-94 and 1997, and 29 were newly identified. The medical evaluation included detailed medical histories, physical exams, 24-hour urinary uranium concentrations, several blood chemistry and hematology tests, neuropsychological testing, neuroendocrine tests, and semen quality. Eight years after exposure, the 13 veterans with retained metal fragments continued to excrete elevated concentrations of urine uranium (0.018 to 39.1 micrograms of uranium per gram creatinine). In contrast, the 37 veterans without retained metal fragments excreted concentrations of uranium that were within the normal range for the general U.S. population (0.002 to 0.231 micrograms of uranium per gram creatinine).

There were 23 veterans who provided urine specimens in all three evaluations in 1993-94, 1997, and 1999. The urinary uranium concentrations tended to be very stable over time. This suggested that the uranium concentration is in a steady state in the body, and the body burden for those with retained fragments is not declining over time. At high concentrations, the kidney is considered the target organ for uranium. Nonetheless, there were no differences found in renal function parameters between the high and low uranium groups, including several functional measures of the proximal tubule, the tissue that is the most sensitive to uranium. Blood chemistry and hematology tests were essentially normal.

There were no significant differences between the high and low uranium groups on the four neuropsychological tests. The authors concluded that the subtle neuropsychological findings that were detected in 1997 have diminished. There were no differences between the high and low uranium groups on five neuroendocrine (hormone) tests (luteinizing hormone, follicle stimulating hormone, prolactin, testosterone, and two thyroid tests). Normal semen analyses were observed in both the high and low uranium groups. The 50 veterans who were examined in 1999 have fathered 35 children since the Gulf War, all without birth defects. The authors concluded that there were "relatively few abnormal clinical findings in this group" of 50 veterans. The medical surveillance of this cohort of DU-exposed veterans will continue indefinitely, and another round of examinations took place in 2001.

2. Hodge, SJ, Ejnik, J, Squibb, KS, McDiarmid, MA, Morris, ER, Landauer, MR, and McClain, DE. Detection of depleted uranium in biological samples from Gulf War veterans. *Military Medicine* 2001 December; 166 (12 Suppl.):69-70. (**Funded by DoD and VA)**

The objective of this study was to demonstrate an assay method that could differentiate DU exposure from exposure to natural uranium, in Gulf War veterans with or without retained metal fragments. (Hodge, et al., 2001) Elevated urinary uranium levels have been demonstrated in soldiers with retained metal fragments, who were exposed to DU in friendly fire incidents. (Hooper, et al., 1999; McDiarmid, et al., 2000; McDiarmid, et al., 2001b) Because of the potential toxicity of DU, there have been concerns about long-term systemic health effects in this cohort of veterans. An assay method that could measure DU exposure would not only be a useful research tool, but it could also be used to ameliorate the concerns of individuals about possible exposures. (Hodge, et al., 2001)

The 14 individuals in this study were a subset of the 50 veterans who were evaluated at the Baltimore VA Medical Center in 1999. (McDiarmid et al., 2001b) Ten veterans had retained metal fragments and four veterans did not. The total uranium concentration in the former group of veterans ranged from more than 1.0 to 39.1 mg uranium per gram creatinine. The total uranium concentration in the latter group of

veterans was less than 0.1 mg uranium per gram creatinine. Isotopic composition of urinary uranium was determined by measuring the ratio of U-235 to U-238, using an inductively coupled plasma mass spectrometer. (Hodge, et al., 2001) The isotopic ratios showed that a large proportion of the uranium in the urine samples was DU, as opposed to natural uranium, in the 10 veterans with retained metal fragments. The proportions of DU ranged from 71 to 98% in these 10 samples. Urine samples with the highest concentrations of total uranium also contained the highest percentages of DU.

The urine samples from the 4 veterans without retained metal fragments showed total uranium concentrations that were representative of normal background levels. There was no evidence of DU in these 4 samples. Using this assay, natural uranium and DU were readily differentiated. This assay could be used to demonstrate the absence of DU in veterans who have concerns about possible exposures; therefore, the assay could be used to ameliorate anxiety in these individuals.

H. Pyridostigmine Bromide

Overview:

Three studies published in 2001 focused on the effects of pyridostigmine bromide (PB), one in humans and two in laboratory animals. The objectives of the first study were "to quantify the type, intensity, and frequency of side effects of low-dose PB, and to examine factors that predict the intensity and frequency of side effects." (Cook, et al., 2001) The objective of the second study was to investigate to what extent administration of PB could affect food motivation in Wistar-Hanover rats, as measured with a progressive-ratio schedule of reinforcement. (van Haaren, et al., 2001a) The objective of the third study was to treat guinea pigs with PB to determine the effects on the blood-brain barrier, and on blood and brain cholinesterase levels. (Lallement, et al., 2001)

Pyridostigmine Bromide-Individual Studies:

1. Cook, MR, Gerkovich, MM, Sastre, A, and Graham, C. Side effects of low-dose pyridostigmine bromide are not related to cholinesterase inhibition. *Aviation, Space, and Environmental Medicine* 2001 December; 72(12):1102-1106. **(DoD-64)**

The objectives of this study were "to quantify the type, intensity, and frequency of side effects of low-dose PB, and to examine factors that predict the intensity and frequency of side effects." (Cook, et al., 2001) The observed side effects of PB were described at two doses, the standard military dose and double the standard dose. Also, the relationship of side effects to cholinesterase activity was evaluated. Current military doctrine is to take PB as a pretreatment for possible exposure to chemical nerve agents, at a dose of 30 mg every 8 hours, for up to two weeks, as long as there is a high risk of attack with chemical weapons. PB has been used since 1955 to treat myasthenia gravis (MG) in doses ranging from 200 to 1400 mg per day. At the lower dose range, the drug is well tolerated by most MG patients. In previous controlled studies in the military setting, few side effects have been reported, however, no previous studies included female volunteers, and none used doses higher than the standard military dose.

A double-blind, cross-over, placebo-controlled design was used. Of the 67 subjects, 33 received 30 mg PB every 8 hours for 13 doses, and 34 received 60 mg on the same schedule. The order of the PB week and the placebo week was counterbalanced. 36 healthy young men and 31 healthy young women participated, who were aged 18-35, and who were volunteers from the Kansas City community. The PB Side Effects Scale was developed for this study, which was a list of 13 symptoms that had been reported as side effects of PB in previous studies, including urination problems, nausea, and diarrhea. These 13 symptoms were embedded in a 32-item list of commonly experienced symptoms, such as rash, dizziness, and headaches (45 symptoms total). Overall, side effects occurred infrequently and they were generally mild, even at the 60 mg dose. Even at the same dose level, however, some subjects reported more side effects than others, when taking both placebo and PB. The most frequently reported symptoms were flatulence (28% of subjects), nausea (19%), and abdominal pain (15%). Some Gulf War veterans reported that they had immediate, intense symptoms after taking the first few PB pills. In contrast, most subjects in this study reported few, if any, side effects after one day of dosing.

When asked to judge whether they had taken PB or placebo during the previous week, subjects were accurate 61% of the time. This accuracy was greater with the 60 mg dose (72%) than for the 30 mg dose (59%). The presence of side effects was a major factor in the subjects' ability to accurately judge whether they had taken PB or placebo the previous week. A multiple regression analysis was performed to determine the factors that were related to reported side effects during the PB week, using the following factors as possible predictors: reported side effects during the placebo week, percent activity of acetylcholinesterase (AChE), percent activity of butyrylcholinesterase (BuChE), dose in milligrams per kilogram of body weight, drug order, and gender. The only factor that significantly predicted side effects during the PB week was side effects during the placebo week. "The most surprising finding was that side effect scores were not greater with higher blood levels of PB or with greater inhibition of either AChE or BuChE activities." The average activity of AChE was 60%, which equals 40% inhibition. 30% inhibition of AChE or greater is optimal, for effective pretreatment for nerve agent exposure.

The authors concluded, "PB is well tolerated by healthy young people, even when twice the recommended military dose is administered." These results were consistent with other controlled studies of the side effects of PB; however, they differed from some studies conducted under battlefield conditions. The authors commented "The observation that, in field studies, side effects are experienced more frequently and are more severe than during laboratory studies implies that symptoms may be exacerbated by the unavoidable physiological and psychological stresses of war."

2. van Haaren, F, Haworth, SC, Bennett, SM, and Cody, BA. The effects of pyridostigmine bromide on progressive ratio performance in male and female rats. *Pharmacology, Biochemistry, and Behavior* 2001a January; 68(1):81-85. **(DoD-37)**

This was the first study to investigate if administration of PB alters the efficacy of food presentation in reinforcement of behavior. The objective of this study was to investigate to what extent administration of PB could affect food motivation in Wistar-Hanover rats, as measured with a progressive-ratio (PR) schedule of reinforcement. (van Haaren, et al., 2001a) On PR schedules, the response requirement is systematically increased by a fixed number of responses after presentation of each reinforcer. The breaking point is defined as the penultimate ratio that the subject completed, before it failed to complete the ultimate ratio within a specific period of time. This breaking point may reflect motivational variables, because it has been shown to vary systematically with increases in food deprivation. Access to food was limited in the rats' home cages. Different doses of PB (vehicle, 3, 10, or 30 mg/kg) were administered by gavage, 30 minutes before the start of an experimental session. Response rates were significantly lower after the 10 and 30 mg/kg doses, but not after the 3 mg/kg dose. All three doses decreased the breaking points, compared to administration of the vehicle, and the differences between the doses were also significant. This effect may be due to decreased food motivation, or it may be due to drug-induced nausea. There were no measurements of blood or brain levels of acetylcholinesterase, therefore, it is unknown whether PB crossed the blood-brain barrier.

3. Lallement, G, Foquin, A, Dorandeu, F, Baubichon, D, Aubriot, S, and Carpentier, P. Subchronic administration of various pretreatments of nerve agent poisoning. I. Protection of blood and central cholinesterases, innocuousness towards blood-brain barrier permeability. *Drug and Chemical Toxicology* 2001 May; 24(2):151-164. **(Not Federally funded-French study)**

The objective of this study was to treat guinea pigs with various drugs, in order to determine the effects on the blood-brain barrier, and on blood and brain cholinesterase levels. (Lallement, et al., 2001) The study drugs included PB, Huperzine A, and physostigmine, with or without scopolamine; however, only the results of the PB experiments are summarized here. PB was administered continuously for 6 days, through a pump that was implanted under the skin. The dose of PB was 5.1 mg per hour. After 6 days of PB treatment, the average percent inhibition of blood AChE was 38%, and the average percent inhibition of blood BuChE was 18%. 30% inhibition of blood AChE or greater is optimal for effective pretreatment for nerve agent exposure. PB treatment caused no inhibition of brain levels of AChE in the hippocampus, striatum, or cortex. This means that after 6 days of continuous treatment, PB did

not cross the blood-brain barrier. The authors concluded that each of the study drugs, including PB, seemed to have a "total innocuousness on the permeability of the blood-brain barrier."

I. Interactions of Exposures (Pyridostigmine Bromide in Combination with Stress, Vaccines, or Other Chemicals; or Interactions of Chemicals, Other than PB)

Overview:

Four laboratory studies published in 2001 focused on the effects of pyridostigmine bromide (PB), in combination with stress, vaccines, or other chemicals. (Kant, et al., 2001; Griffiths, et al., 2001; van Haaren, et al., 2001b; and Abou-Donia, et al., 2001b)

Two laboratory studies published in 2001 focused on the interactions of chemicals, other than PB (DEET and permethrin). (Abou-Donia, et al., 2001a; Abdel-Rahman, et al., 2001)

Stress alone appears to induce significant changes in blood-brain barrier (BBB) permeability in young rats and mice, but little or no changes in adults. Reports have shown effects of exogenous stressors like forced swim, restraint, or heat stress on the entry of radioactive tracers, dyes, or viruses into the CNS. These studies have been conducted primarily in young, immature rodents. (Sharma, et al., 1991; Sinton, et al., 2000) The overall conclusion in a recent study was "There is no evidence that exogenous stress increases BBB permeability in mature rodents." (Sinton, et al., 2000)

The one exception, regarding adult rodents, was a study by Friedman that suggested that pyridostigmine bromide (PB) could enter the brain of adult mice subjected to forced swimming stress. (Friedman, et al., 1996) Friedman demonstrated that the dose of PB required to produce 50% inhibition of brain acetylcholinesterase (AChE) activity in stressed FVB/n mice was only 1% of the dose of PB required to produce 50% inhibition in non-stressed mice. However, there is some experimental evidence that the FVB/n mouse strain may have an unusually permeable BBB. (Telang, et al., 1999) Furthermore, the intensity of the reported effect in Friedman's study (more than 50% inhibition) could not be easily explained by the limited and localized changes in BBB permeability that had previously been reported to be induced by stress. (Sharma, et al., 1991)

Several studies have recently evaluated whether stress can increase BBB permeability, and can therefore enhance penetration of PB into the brain. These have included several species and strains of animals: 3 different strains of mice (Telang, et al., 1999; Chaney, et al., 1999; Grauer, et al., 2000); guinea pigs (Lallement, et al., 1998); and 3 strains of rats (Sinton, et al., 2000; Chaney, et al., 2000; Kant, et al., 2001). These studies have included several types of acute stressors: forced swimming stress (Telang, et al., 1999; Grauer, et al., 2000; Sinton, et al., 2000); heat stress (Lallement, et al., 1998; Sinton, et al., 2000); severe cold stress (Grauer, et al., 2000); restraint stress (Sinton, et al., 2000; Kant, et al., 2001); foot shock stress (Kant, et al., 2001); and chemical stress (coadministration of high doses of DEET) (Chaney, et al., 1999; Chaney, et al., 2000).

All of these studies since 1998 have reached the conclusion that stress does not increase BBB permeability to PB, and that PB does not penetrate the brain, even at lethal doses. A recent conclusion was "The preponderance of the evidence by a number of laboratories now points to some unknown experimental artifact associated with the original positive report [Friedman, et al., 1996]." (Kant, et al., 2001) In addition, Sinton, Haley, and colleagues concluded "to the extent that cross-species comparisons are valid" between humans and rodents, "the effects of stress on BBB permeability to PB are unlikely to explain the chronic CNS symptoms reported by some Gulf War veterans." (Sinton, Haley, et al., 2000) This conclusion is particularly noteworthy because one of the authors, Robert Haley, has previously reported an association between a history of PB use and long-term CNS symptoms, based on a questionnaire administered to a small group of Gulf War veterans. (Haley, et al., 1997)

These recent findings about PB and stress are consistent with the conclusion of a recent White House report on illnesses in Gulf War veterans, as follows: "Several more recent studies have failed to reproduce this finding [of Friedman's study in 1996] using a variety of species, a variety of stressful stimuli, and extremely high

doses of PB. If PB does not cross the BBB, it is very unlikely to cause changes in brain function." (White House, 2000)

Interactions of Exposures-Individual Studies:

Interactions of PB in Combination with Stress, Vaccines, or Other Chemicals-Individual Studies:

Four laboratory studies published in 2001 focused on the effects of pyridostigmine bromide, in combination with stress, vaccines, or other chemicals. (Kant, et al., 2001; Griffiths, et al., 2001; van Haaren, et al., 2001b; and Abou-Donia, et al., 2001b)

1. Kant, GJ, Bauman, RA, Feaster, SR, Anderson, SM, Saviolakis, GA, and Garcia, GE. The combined effects of pyridostigmine and chronic stress on brain cortical and blood acetylcholinesterase, corticosterone, prolactin, and alternation performance in rats. *Pharmacology, Biochemistry, and Behavior* 2001 October-November; 70(2-3):209-218. **(DoD-79)**

The objective of this study was to use around-the-clock intermittent signaled foot shock to investigate the potential synergistic effects of chronic stress and PB on the behavior of male Sprague-Dawley rats. (Kant, et al., 2001) Rats were trained to perform an alternation lever-pressing task to earn their entire daily food intake. This task relied on working memory, and previous experiments had shown that chronic stress caused impairment of this task. The rats were then implanted with pumps containing vehicle or PB. The dose of PB was 1.5 mg/kg/day. 24 of the 72 rats were trained to escape the signaled foot shock (avoidance-escape group); 24 other rates were yoked, to prevent escape from the foot shock (yoked-stressed group); and the other 24 rats were not exposed to the foot shock (unstressed group). Shock trials were intermittently presented in the home cage for 24 hours per day for 3 days, while alternation performance continued to be measured. PB caused inhibition of blood AChE of about 50%, but no inhibition of brain AChE. Alternation performance was impaired on the first day of stress, but then it recovered. PB alone did not impair alternation performance. PB plus stress did not increase impairment of alternation performance, compared to stress alone. Corticosterone was significantly increased in the yoked stress group, compared to unstressed controls. The authors concluded that there was no evidence that a combination of stress and PB acted synergistically, and that PB did not "exacerbate the effects of stress on performance or levels of stress hormones." They also stated that chronic PB administration at doses that caused 50% inhibition of blood AChE did "not penetrate the blood-brain barrier in chronically stressed rats or affect a test of working memory in rats."

2. Griffiths, GD, Hornby, RJ, Stevens, DJ, Scott, LA, and Upshall, DG. Biological consequences of multiple vaccine and pyridostigmine pretreatment in the guinea pig. *Journal of Applied Toxicology* 2001 January-February; 21(1):59-68. **(Funded by UK Ministry of Defence)**

The objective of this study was to simulate the PB and multiple vaccine protocols experienced by UK forces during the Gulf War, by modeling a "worst case" situation in which PB and all ten vaccines were given to guinea pigs within a short period of time. (Griffiths, et al., 2001) UK troops received some or all of the following ten vaccines: polio, hepatitis B, yellow fever, cholera, typhoid, meningococcal, tetanus, anthrax, pertussis, and plague. Guinea pigs were selected because of the extensive experimental literature on the effects of PB on this animal. Four groups of eight animals were treated with vehicle, 5%, 10%, or 20% of the human dose of vaccines, respectively. PB or saline was delivered by an implanted pump for 28 days. The average inhibition of blood AChE was 30%. Body weight, temperature, immunological responses, biochemical indices, and spontaneous activity were monitored for 72 days. There were no remarkable findings in any of these parameters. There was no histological evidence of any significant pathological abnormalities in any of the tissues. In the group that received 20% of the human dose of vaccines, there was a 5% decrease in body weight, which was not considered clinically significant. All vaccine dosage groups showed some specific antibody responses against all the bacterial pathogens. Animals in all groups remained generally healthy and active, without visible adverse signs throughout the study. A follow-up study with marmosets (monkeys) has begun, which includes the same experimental plan, but also includes

evaluation of cognitive behavior and sleep patterns.

3. van Haaren, F, Haworth, SC, Bennett, SM, Cody, BA, Hoy, JB, Karlix, JL, and Tebbett, IR. The effects of pyridostigmine bromide, permethrin, and DEET alone, or in combination, on fixed-ratio and fixed-interval behavior in male and female rats. *Pharmacology, Biochemistry, and Behavior* 2001b May; 69(1-2):23-33. (**DoD-37)**

The behavioral effects of PB, permethrin, and DEET in combination may exceed the effects of the individual chemicals. The objective of this study was to assess the behavioral effects of PB, permethrin, and DEET, alone and in combination, on well-established performance of learned tasks in Sprague-Dawley rats. (van Haaren, et al., 2001b) 15 to 30 minutes before the start of an experimental session, PB and DEET were given by gavage, and permethrin was injected intraperitoneally. PB alone decreased response rates in a dose-dependent manner, equally in both male and female rats. Only the highest dose of permethrin alone decreased response rates, more so in male rats than females. Only the highest dose of DEET alone decreased response rates, more so in female rats than males. Of the possible combinations of chemicals, only two combinations produced a significant effect on response rates. Low-dose PB combined with low-dose permethrin, or low-dose PB combined with low-dose DEET, decreased response rates in male rats only. The lack of synergistic effects of other combinations of chemicals may be due to the fact that, in most other cases, administration of single chemicals resulted in opposite behavioral effects. The authors concluded that some combinations of low doses of PB, permethrin, and DEET disrupted well-established, schedule-controlled behavior in rats, in a gender-dependent manner. The mechanism of these behavioral effects is unknown. There were no measurements of blood or brain levels of acetylcholinesterase, therefore, it is unknown whether PB crossed the blood-brain barrier.

4. Abou-Donia, MB, Goldstein, LB, Jones, KH, Abdel-Rahman, AA, Damodaran, TV, Dechovskaia, AM, Bullman, SL, Amir, BE, and Khan, WA. Locomotor and sensorimotor performance deficit in rats following exposure to pyridostigmine bromide, DEET, and permethrin, alone and in combination. *Toxicological Sciences* 2001b April; 60(2):305-314. **(DoD-75)**

The objective of this study was to investigate the effects of PB, DEET, and permethrin, alone or in combination, on the sensorimotor behavior and central cholinergic system of male Sprague-Dawley rats. (Abou-Donia, et al., 2001b) The rats were treated with DEET or permethrin dermally for 45 days. During the last 15 days of the 45-day period, some of the rats received PB by gavage (dose of 1.3 mg/kg/day). Sensorimotor ability was assessed with a battery of tests on days 30 and 45. Animals treated with PB alone, or PB in combination with DEET and permethrin, showed a significant impairment in beam-walk score and beam-walk time, compared to controls. All chemicals, alone or in combination, caused significant impairments in incline plane testing and in forepaw grip. All other behavioral tests were not affected by the various treatments, including postural reflexes, limb placing, or vibrissae touch. On day 45, the animals were euthanized, and plasma BuChE and brain AChE levels were measured. There was no inhibition of plasma BuChE in any of the treatment groups. No blood AChE levels were reported, which makes it difficult to compare this study with previous studies. Brain AChE activity was measured in the cortex, brainstem, midbrain, and cerebellum. Treatment with PB alone caused only a moderate inhibition in AChE activity in the brainstem. DEET alone caused a significant increase in brainstem AChE activity. Permethrin alone caused a significant increase in cortical AChE activity. PB, DEET, and permethrin together caused a significant inhibition of AChE in brainstem and midbrain. The authors concluded that exposure to PB, DEET, permethrin, alone or in combination, led to neurobehavioral deficits and region-specific alterations in AChE. They stated that "The contribution of cholinergic changes to the behavioral deficit following treatment with these chemicals is not clear at the moment, as these changes may involve a combination of mechanisms related to central and peripheral or neuromuscular system." There was no follow-up to determine if the behavioral changes due to the chemicals were prolonged or reversible with time, which is relevant to the possible effects in humans. In addition, these results cannot be directly extrapolated to Gulf War veterans, because it is highly unlikely that troops experienced continuous exposures to PB, DEET, and/or permethrin for 45 days or longer.

Interactions of Chemicals, Other than PB-Individual Studies:

Two laboratory studies published in 2001 focused on the interactions of chemicals, other than PB (DEET and permethrin). (Abou-Donia, et al., 2001a; Abdel-Rahman, et al., 2001)

1. Abou-Donia, MB, Goldstein, LB, Dechovskaia, A, Bullman, S, Jones, KH, Herrick, EA, Abdel-Rahman, AA, and Khan, WA. Effects of daily dermal application of DEET and permethrin, alone and in combination, on sensorimotor performance, blood-brain barrier, and blood-testis barrier in rats. *Journal of Toxicology and Environmental Health* 2001a April 6; 62(7):523-541. **(DoD-75)**

The objective of this study was to investigate the effects of daily dermal application of DEET and permethrin, alone or in combination, on the permeability of the blood-brain barrier (BBB) and on sensorimotor performance in male Sprague-Dawley rats. (Abou-Donia, et al., 2001a) Groups of rats were treated with a daily dermal dose of 3 different doses of DEET or 3 different doses of permethrin for 60 days. A control group of rats was treated with daily exposures to vehicle (ethanol). Permethrin alone produced no effects on BBB permeability. DEET alone caused a decrease in BBB permeability in the brainstem. The combination of DEET and permethrin caused a significant decrease in BBB permeability in the brain cortex. The animals underwent a battery of functional behavioral tests at 30, 45, and 60 days after exposure to evaluate their sensorimotor abilities. There were no effects of DEET or permethrin, alone or in combination, on simple sensorimotor reflexes. However, either chemical, alone or in combination, caused a deficit in complex sensorimotor performance, in a dose-dependent and time-dependent manner. These behavioral effects could be mediated centrally, peripherally, or through a combination. The authors suggested a peripheral mechanism of action, at least partially. The authors also published two related biochemical studies in rats in 2001. (Abu-Qare and Abou-Donia, 2001; Abu-Qare, et al., 2001)

2. Abdel-Rahman, A, Shetty, AK, and Abou-Donia, MB. Subchronic dermal application of N,N-diethyl m-toluamide (DEET) and permethrin to adult rats, alone or in combination, causes diffuse neuronal cell death and cytoskeletal abnormalities in the cerebral cortex and the hippocampus, and Purkinje neuron loss in the cerebellum. *Experimental Neurology* 2001 November; 172(1):153-171. **(DoD-75)**

The objective of this study was to determine the anatomical effects of subchronic dermal application of DEET and permethrin on the brains of adult male Sprague-Dawley rats. (Abdel-Rahman, et al., 2001) Histopathological alterations were evaluated after a daily dermal dose of DEET alone, permethrin alone, or a combination, for 60 days. Quantification of healthy (or surviving) neurons in the cerebral cortex, hippocampus, and cerebellum revealed significant reductions in all three treatment groups. In addition, rats that received DEET alone or permethrin alone demonstrated a significant number of degenerating neurons in the same brain regions. The authors concluded that all three types of treatment led to a diffuse neuronal cell death in the cerebral motor cortex, hippocampus, and cerebellum. There were also cytoskeletal abnormalities in the surviving neurons that could lead to compromised brain function. The various abnormalities in the motor cortex and the hippocampus could lead to behavioral abnormalities, especially motor deficits and memory dysfunction, respectively. These results cannot be directly extrapolated to Gulf War veterans, because it is highly unlikely that troops experienced continuous exposures to DEET and/or permethrin for 60 days or longer.

III. RESEARCH FUNDING TRENDS

A. Overview

Appendix A provides details of the Gulf War Veterans' Illnesses Research Database. It was last updated during the first quarter of Fiscal Year 2002 (through December 31, 2001). Research projects are grouped according to the Department that is responsible for the conduct or sponsorship of the research.

Each entry in the database includes:

- Project Title
- Responsible Federal Agency
- Study Location
- Project Start-up Date
- Project Completion Date (estimated if ongoing)
- Overall Objectives of Project
- Specific Aims of Project
- Methods of Approach
- Expected Products (Milestones)
- Current Status/Results
- Publications

Two descriptors can approximately categorize each research project. The first descriptor is a series of **Research Focus Areas.** The research focus areas are categorized as follows:

- Prevalence and risk factors for symptoms and alterations in general health status
- Brain and nervous system function
- Chemical weapons
- Environmental toxicology (e.g. studies focused on specific environmental toxicants such as pesticides, oil well fires, etc.)
- Reproductive health
- Depleted uranium
- Leishmaniasis
- Immune function
- Pyridostigmine bromide
- Mortality experience
- Interactions of exposures (chemical, biological, pharmacological, physiological, etc.)
- Prevention of diseases (i.e. studies that will produce knowledge that could lead to disease prevention strategies)
- Treatment
- Diagnosis (i.e. studies that will improve the ability to diagnose previously unexplained conditions, or to better refine diagnoses with new tools)

Each project is assigned up to three focus areas as categorical descriptors. This allows accounting for projects that cover multiple focus areas. For example, a project on the neurophysiological effects of exposure to sarin in animals would have a focus on the brain and nervous system, and a focus on chemical weapons. The number of focus areas (between one and three) assigned to a project depends on the project itself.

The other descriptor for each project is **Research Type**. The Federal Government defines **Research** as systematic investigation designed to develop or contribute to generalizable knowledge. Each research project on Gulf War veterans' illnesses uses a method of approach to test a specific research hypothesis. Approaches range in type from **mechanistic research**, addressing potential biological mechanisms of causation, to **clinical** and **epidemiological research** that attempt to determine illness prevalence and risk factors. Although precise categorization of research types can be difficult because of overlapping methodologies, research projects can be divided into the following general types:

MECHANISTIC RESEARCH: Research into underlying mechanisms of diseases and illnesses using *in vitro* and *in vivo* models.

CLINICAL RESEARCH: Application of an intervention, such as in a controlled drug trial, or use of methodologies such as case-control studies to define risk factors for disease.

EPIDEMIOLOGY RESEARCH: Study of the distribution and determinants of disease in human populations. It includes population-based studies focused on outcomes such as mortality, symptoms, hospitalizations, etc., using devices such as postal surveys, telephone interviews, and reviews of medical records.

In addition to the research on Gulf War veterans' illnesses, the RWG also tracks development work. In general, **development** is the systematic use of the knowledge or understanding gained from research directed toward the production of materials; devices; systems; or methods, including design, development, and improvement of prototypes and new processes.

Within the context of Gulf War veterans' illnesses, the RWG categorizes activities as **development** as follows:

DEVELOPMENT: An activity that satisfies the general definition of development described above, and is directed toward new biologically based prevention, intervention, and treatment measures.

The Gulf War Veterans' Illnesses Research Database catalogs only research and development activities that either directly involve Gulf War veterans, or has been initiated to answer specific questions about risk factors. An example of the latter is a research project using animal models to determine health effects of low-level chemical warfare agents. The database does not account for the vast accumulated knowledge derived from the nation's investment in biomedical research over the past 50 years.

The Gulf War Veterans' Research Database only contains research that is Federally sponsored. This includes research conducted by Federal scientists, as well as that by non-federal scientists supported by Federal research funds through grants, contracts, and cooperative agreements. It is not possible to accurately track research efforts that fall within the private sector or otherwise outside of the purview of the Federal Government. Nonetheless, the RWG attempts to stay abreast of all research relevant to Gulf War veterans' illnesses. The RWG accomplishes this by monitoring the peer-reviewed published scientific literature, attending scientific meetings, and even using newspaper reports and personal accounts of researchers.

Regardless of the source of support for particular research projects, the RWG will ensure that all research, which has been published in peer-reviewed scientific literature, will be used in formal assessments of the nature and causes of Gulf War veterans' illnesses. A number of projects that were not Federally funded have been reviewed in Section II Research Results of this *Annual Report to Congress*.

An interim assessment of the nature and causes of illnesses in Gulf War veterans was included in Appendix C of the *Annual Report to Congress for 2000*. (MVHCB, 2001a) In 1996, the RWG identified 21 major research questions. The comprehensive Gulf War research portfolio has addressed each of these questions, and relevant results have been published on each one. Appendix C provided a formal assessment of the progress made on each of these 21 questions.

The following sections provide a quantitative overview of the current research portfolio on Gulf War veterans' illnesses and the evolution of the portfolio over time since 1994. Topics that are covered include overall research expenditures from 1994-2002 (projected), and the types and areas of research in which the Federal Government has invested.

B. Research Funding

All current Federal research projects directly related to Gulf War veterans' illnesses are sponsored by VA, DoD, or HHS. From 1994 through 2002, the Departments have sponsored 224 distinct research projects on Gulf War veterans' illnesses. This does not include research projects that recently have been selected for funding, but are currently in final contract negotiations. This also does not account for anticipated projects arising from competition of proposals submitted in response to new initiatives, such as a DoD Broad Agency Announcement (BAA) for 2002.

A table in Appendix A lists all of the research and development projects and programs supported now or in the past by the Federal Government. The appropriated funds, centrally distributed to each program or project, are shown in the fiscal years that funds were obligated. Many extramural projects are multi-year efforts for which funds are obligated at the beginning of the project period.

Table III-1 is a summary of research expenditures by DoD, VA, and HHS between FY94 and FY01, and a projection of funding into FY02. Currently, the Federal Government is projecting cumulative expenditures of $212.6 million for research from FY94 through FY02. As of September 30, 2001, 124 projects were completed. As of September 30, 2002, a total of 159 projects will be completed (71% of total of 224 projects), and 65 projects will be ongoing.

Table III-2 is a year-by-year account of new and completed projects**.**

Table III-1. Funding for Research FY'94-'02 in $Millions

Department	FY'94	FY'95	FY'96	FY'97	FY'98	FY'99	FY'00	FY'01	FY'94-'01	FY'02
DoD	$6.5	$11.0	$11.9	$28.9	$13.2	$23.5	$24.8	$22.0	$141.8	$12.0
VA	$1.2	$2.3	$3.9	$2.8	$4.7	$9.0	$12.0	$8.4	$44.3	$3.7
HHS	$0.0	$2.5	$1.6	$0.0	$1.6	$1.6	$1.6	$1.0	$10.0	$0.8
Total	**$7.7**	**$15.8**	**$17.4**	**$31.7**	**$19.5**	**$34.2**	**$38.4**	**$31.4**	**$196.1**	**$16.5**

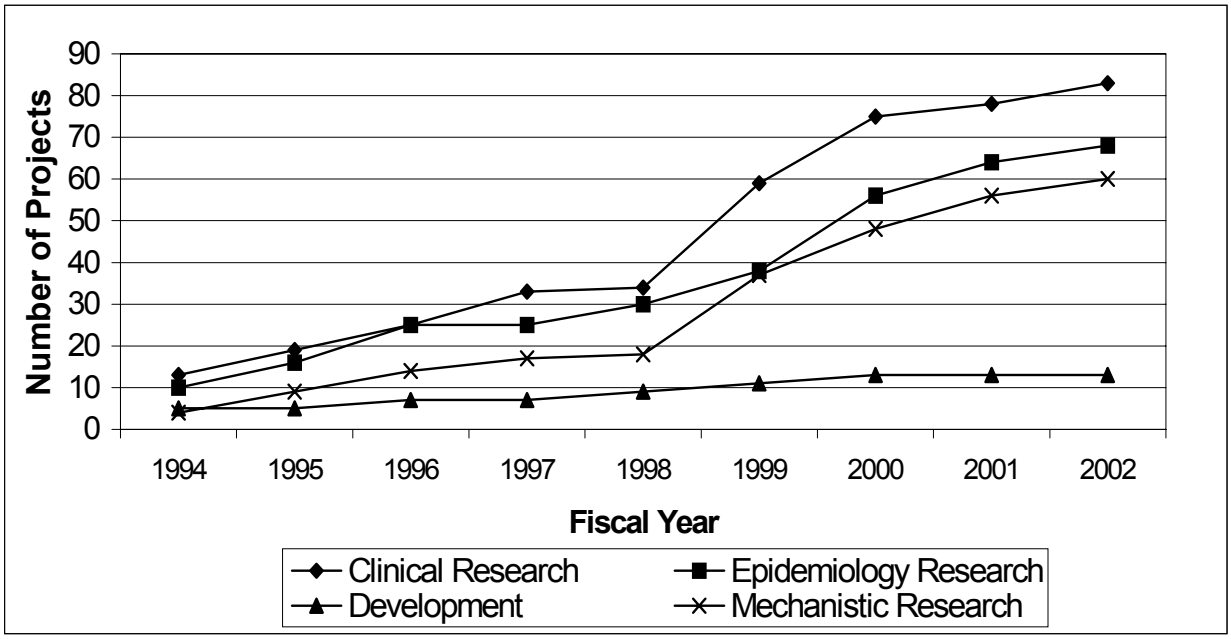
Table III-1. does not include funds to cover operational costs for administration, infrastructure, etc. For example, the VA research appropriation does not pay for clinician/investigator salaries. In addition, Table III-1. does not include funding for activities performed by members of the RWG (salaries, travel, etc.). The FY'02 funds are estimated, and they do not include funds for anticipated or future solicitations.

Table III-2. Number of New and Completed Projects by Year*

Fiscal Year	New	Completed
1992-1994	62	3
1995	21	8
1996	16	4
1997	36	10
1998	17	15
1999	30	16
2000	14	42
2001	15	26
2002**	13	35

*For programs/centers with multiple projects, each project is counted as an individual project for accounting purposes.
** Includes all projects that are planned to start or finish between 10/01/01 and 9/30/02.

Figure III-1. Cumulative number of research projects by research type (1994-2002).



C. Diversity of Research Approaches

The funds that have been invested in research on Gulf War veterans' illnesses over the years have gone into a broad-based portfolio with respect to research type and research focus area. **Figure III-1** illustrates the number of projects of each research type for each year since FY94. On average, epidemiology and clinical research have each comprised approximately one third of the total number of projects. The remaining third has been divided between mechanistic research and development, with the larger share going to mechanistic research.

The distribution of projects across different research focus areas is illustrated in **Figure III-2**. Projects for each focus area are categorized by the focus areas, which are listed as one of the three areas assigned to each project. The total number of projects by research focus areas is shown in Figure III-2 in two ways. For each focus area, a black bar represents the total number of projects for which that focus area is listed as primary. A clear bar represents the total number of projects for which that focus area is listed as secondary or tertiary. Thus the total height of a bar represents the total number of projects for which the focus area is listed as primary, secondary, or tertiary. By showing the data this way, the multiplicative effects of research investments are demonstrated. For example, a project that examines the effects of Pyridostigmine Bromide on the Brain and Nervous System is counted under both of these focus areas.

As can be seen in **Figure III-2**, the overall emphasis of research has been greatest in the focus areas of the Brain and Nervous System Function and in Symptoms and General Health Status. This reflects the focus of epidemiological efforts on the prevalence of symptoms and illnesses in Gulf War veterans, and the focus of clinical research efforts on risk factors for illnesses. The focus on the brain and nervous system is a result of both the dominance of health complaints in this area, and the fact that many of the potential exposures in the Gulf were to neurotoxic chemicals.

The number of research projects in the various research focus areas has changed over time since 1994 as a reflection of the evolution of issues centered on Gulf War veterans' illnesses. The relatively greater increase over the years of research on chemical warfare agents, pyridostigmine bromide, and interactions of chemicals is noteworthy. These increases are an outgrowth of increased concern over the health risks posed to veterans by exposures to multiple toxic agents at low concentrations.

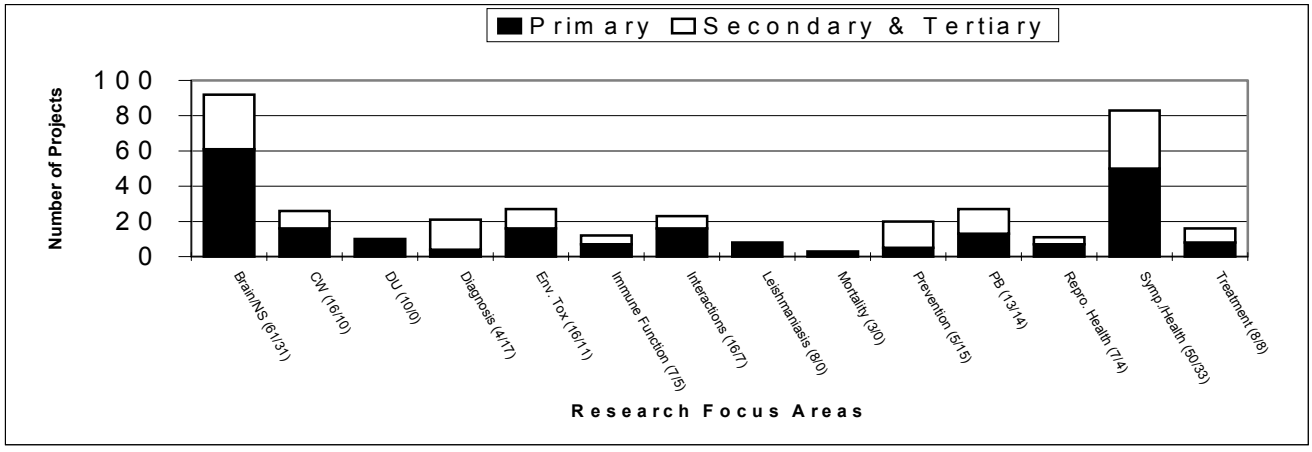


Figure III-2. Number of projects in each research focus area. Closed bars represent the number of projects with the focus area as primary; open bars represent the number of projects with the focus area as either secondary or tertiary. The first number within the parenthesis represents the number of projects with a primary research focus area. The second number represents the number of projects with a secondary or tertiary research focus area.

IV. NEW RESEARCH PROJECTS AND INITIATIVES

Several new research projects and initiatives that have been undertaken since last year's *Annual Report to Congress* are highlighted in this Section. These include the awarding of new research projects and the development of new research initiatives. In addition, this Section provides an update of important accomplishments in 2001 for key research projects and initiatives.

Many of the new research projects and initiatives are responsive to recommendations from a variety of sources, including the Presidential Advisory Committee on Gulf War Veterans' Illnesses (PAC, 1996a; PAC, 1996b; PAC, 1997); the Institute of Medicine Committee on the Health Consequences of Service During the Persian Gulf War (IOM, 1995; IOM, 1996); the Senate Veterans' Affairs Committee (SVAC, 1998); the Presidential Special Oversight Board (PSOB, 2000); and the RWG (PGVCB, 1995b; PGVCB, 1996b).

A. NEW RESEARCH PROJECTS

Thirty-one new projects were added to the research portfolio in 2001. Three groups of these projects are highlighted in this section:

- sixteen research projects funded by the 2000 DoD Broad Agency Announcements;
- a multi-center treatment trial of PTSD in women, jointly funded by VA and DoD; and
- two new research projects on effective risk communication methods for active-duty service personnel and veterans, funded by CDC.

IV.A.1. New Projects Funded by the 2000 DoD Broad Agency Announcements

In 1998, DoD established new funding for programmed research. The purpose of this program element funding is to address issues of Gulf War veterans' illnesses, which may also be of concern in future deployments. These include issues identified in both the research plans of the PGVCB and the Presidential Review Directive 5. (PGVCB, 1995b; PGVCB, 1996b; NSTC, 1998) This funding is approximately $20 million per year for fiscal year 1999 through fiscal year 2002, and $10 million per year thereafter. This funding makes it possible to organize multi-year research and improves the ability to respond to new research needs based on discoveries in the currently funded programs. The program is guided by a tri-service DoD panel and coordinated with the RWG.

The overall objective of this effort is to enhance Force Health Protection in future deployments, through research specifically targeted to solving problems that emerged from service in the Gulf War. Specific research areas include:

1. prevention and treatment of persistent stress symptoms;
2. methods to assess health hazards from toxic chemicals and mixtures and to monitor exposures;
3. improved safety assessments of medical materiel, including potential interactions in operational environments; and
4. epidemiological studies to continue long-term follow-up of Gulf War veterans and to improve health status monitoring in future deployments.

In coordination with the RWG, DoD developed a new research initiative for Fiscal Year 2000. Under this initiative, DoD solicited new research proposals for studies consistent with current concepts of Force Health Protection. There were four Broad Agency Announcements (BAAs), each with a deadline of July 26, 2000.

The four specific requests focused on the following areas of research interest:

1. Epidemiological Investigations of Deployment Health Monitoring Methods

The purpose of these epidemiological studies is to fill critical knowledge gaps for monitoring soldier health during deployments. Threats to health during deployments might include psychological stress, toxic chemical exposures, environmental stressors, and infectious agents. The focus is on physiologically based methods to assess deployment health consequences, through a demonstrated change in health. Projects are required to have a strong biological basis (i.e., objective measurements instead of subjective/questionnaire assessments). Studies are specifically sought in four topic areas:

a. psychological health status, including establishment of mental health baselines of military populations;
b. practical methods for large-scale studies to assess changes in male and female reproductive fertility;
c. clinical illness associated with high frequency of deployments or perceived stress of deployments; and
d. coping strategies used by military personnel to alleviate symptoms associated with Gulf War deployment (e.g., alcohol or complementary and alternative medicine).

2. Deployment Stress Health and Performance Consequences

These studies focus on the effects of psychological stress on cognitive and physiological consequences. Studies should quantify the association between clinical health outcomes or militarily-relevant performance measures and various types of stress, which might be typically encountered in military field deployments (e.g., isolation, family separation, anxiety, inadequate sleep). The studies should explore biological stress measures, which may be useful predictors of health and performance decrements.

3. Biochemical and Physiological Markers to Assess Toxic Chemical Exposures and Health Effects in Deployed Military Personnel

These studies focus on applied physiologically based methods and techniques for assessment of toxic chemical exposures in deployed military personnel. The research should improve current methods and techniques or identify and develop new, readily applied, methods and techniques. Specifically, studies must identify and develop biological markers of exposure that enhance environmental monitoring or provide markers of effect related to exposures of individual service members. Methods and techniques should be applicable to risk assessment or health surveillance of toxic chemicals and chemical mixtures that are a concern in military deployments. Specific chemicals of interest include petrochemical products (including JP8 fuel), insecticides, insect repellents, and Chemical Agent Resistant Coating (CARC).

4. Toxicity of Militarily Relevant Heavy Metals

These studies focus on biological effects of heavy metals currently used or contemplated for use in armor and as armor penetrators. These include tungsten and tungsten alloys, depleted uranium, depleted uranium and titanium alloys, and oxidation products of these metals and their alloys. Inclusion of positive (e.g. lead) and negative (e.g. tantalum) controls should be considered in study designs. Outcomes of special interest include identification of mechanisms of injury to pulmonary, hepatic, renal, and nervous systems from particulate and solubilized forms; and localized soft tissue responses produced by embedded fragments (distinguishing foreign body, radiation, toxicological, and acute phase responses). Exposures should be based on realistic scenarios, and should consider current pharmacokinetic and pharmacodynamic knowledge of the metal or alloy under study. Epidemiological studies could be included based on exposure models.

A total of 62 proposals were submitted in response to these 4 BAAs. These proposals were scientifically peer reviewed by the American Institute of Biological Sciences. Highly meritorious proposals were chosen for funding by DoD program review and then were referred to the RWG for secondary review, based on interagency programmatic relevance. This review process is detailed in Section V Research Management. In early 2001, funding decisions were made and DoD undertook contract negotiations with principal investigators. The scope of work and funding level for each project were finalized by late 2001.

As a result of these four solicitations, 16 new DoD-funded projects were initiated in 2001, at a total cost of $16.74 million. There were 2 projects related to Epidemiological Investigations, 3 projects related to Deployment Stress, 7 projects related to Biochemical Markers, and 4 projects related to Heavy Metals. Table IV.1. lists each of these 16 projects and provides brief summaries of their research objectives.

Table IV.1. New Projects for 2001 Funded by the DoD Broad Agency Announcements

DoD Project Number	Principal Investigator	Institution	Title	Research Objective
Biomarkers of Chemical Exposures and Health Consequences				
DoD-134	Bruce Hammock	University of California at Davis	Identification and Development of Biological Markers of Human Exposure to the Insecticide Permethrin	Develop a field-usable biological monitoring method to detect metabolites of permethrin in urine, indicating dermal absorption of the pesticide in individuals. This permits rapid detection of overexposure to permethrin, which could be used in surveillance and risk assessment studies.
DoD-135	Oksana Lockridge	University of Nebraska Medical Center	Biochemical Markers for Exposure to Low Doses of Organophosphorus Insecticides	Investigate additional sites of action of anticholinesterase agents in relation to potential contributions to neurological dysfunction. This involves the novel acetylcholinesterase(AChE)-knockout mouse model and identification of the non-AChE target proteins.
DoD-136	Charles Thompson	University of Montana at Missoula	A Mechanism-Based, Molecular Fingerprint Strategy for Detecting Biomarkers of Organophosphate Exposure	Develop a systematic approach (mechanism-based molecular fingerprint strategy) to identify short-term biomarkers of exposure to OP anti-cholinesterase compounds. This will also provide an approach to defining the mechanism of non-cholinergic effects of organophosphate (OP) chemicals.
DoD-137	Dan Noort	TNO Prins Maurits Laboratory	Low Level Exposure to Sulfur Mustard: Development of a SOP for Analysis of Albumin Adducts and of a System for Non-Invasive Diagnosis on Skin	Increase sensitivity of assay methods for sulfur mustard adducts, standardize and simplify the procedure, and test its performance on tissue from animals exposed to sulfur mustard. This will improve detection methods for low -level sulfur mustard exposure.
DoD-138	Barry Wilson	University of California at Davis	Improving Blood Monitoring of Enzymes as Biomarkers of Risk from Anticholinergic Pesticides and Chemical Warfare Agents	Study several proven methods for monitoring cholinesterase activity in blood to optimize and harmonize assays among clinical laboratories. This addresses the need for standardized methodology for monitoring high-risk personnel for exposure to anti-cholinergic agents.
DoD-139	Ya Liu	Boston University	Assessment of the Role of Stress-Activated Kinase in the Pathogenesis of Gulf War Illness	Evaluate the role of multiple stressor-associated signaling pathways as mechanisms contributing to neurotoxicity. This also includes determining feasibility of therapeutic interventions targeting these specific kinase pathways that affect acetylcholine synthesis and storage.
DoD-146	Brian Lukey/ Craig Hyams	U.S. Army Medical Research Institute of Chemical Defense	Assessment of Toxicological Assay Methods and Chemical Exposures Among a Cohort of US Marines Deployed in the Gulf War	Analyze 100 paired pre- and 2 day post-Gulf War deployment serum samples from Marine veterans for chemical warfare agents, OP pesticides, sulfur mustard, and vanadium (for smoke exposure). Blinded comparisons will be made between CDC and TNO laboratory assay results. Positive findings may lead to expanded testing of 800 additional samples.
Toxicology of Heavy Metal (Depleted Uranium and Tungsten Alloys)				
DoD-127	Fletcher Hahn	Lovelace Biomedical and Environmental Research Institute	Depleted Uranium Fragment Carcinogenicity: Extrapolation of Findings in Rodents to Man	Identify the nature of observed DU-induced rodent tumor formation and identify early markers of neoplastic changes that can be applied to man.
DoD-128	Bernard Jortner	Virginia Polytechnical and State University	Multifactorial Assessment of Depleted Uranium Neurotoxicity	Study the distribution of DU in brain regions and study behavioral and physiological changes in stressed animals with and without embedded fragments to clarify the neurotoxic potential of embedded DU.

Table IV.1. New Projects for 2001 Funded by the DoD Broad Agency Announcements (Continued)

DoD-129	Johnnye Lewis	University of New Mexico Health Science Center	Inhalation of Uranium Oxide Aerosols: CNS Deposition, Neurotoxicity, and Role in Gulf War Illness	Investigate the potential for inhaled uranium oxide aerosols to penetrate the nose-brain barrier, distribute through the central nervous system, and produce neurotoxic responses. Compare these toxic effects to thresholds for effects on kidneys and lung to determine most likely health outcomes to evaluate in exposed soldiers.
DoD-130	Alexandra Miller	Armed Forces Radiobiology Research Institute	Carcinogenicity and Immunotoxicity of Embedded Depleted Uranium and Heavy-Metal Tungsten Alloys in Rodents	Characterize changes in immune function and carcinogenic response at DU- and tungsten-alloy fragment implantation sites and at distant sites to determine if the metals pose significant carcinogenic risks
Deployment Stress Health and Performance Consequences/Epidemiological Investigations of Deployment Health Monitoring Methods				
DoD-131	Michael Weiner	Northern California Institute For Research and Education	Magnetic Resonance and Spectroscopy of the Human Brain in Gulf War Illnesses	Test the hypothesis that ill Gulf War veterans have metabolic and/or morphological changes in their brain, not accounted for by PTSD, alcohol abuse, and depression. This project independently tests the findings of brain biochemical changes reported by Haley.
DoD-132	Lawrence Adler	University of Colorado Health Science Center	Impaired Auditory Sensory Gating, Acoustic Startle Response: Effects of Long and Short Deployments on Army Combat Readiness	Evaluate whether objective neurophysiological parameters (brain wave recordings) can measure the impact of long (>6 months) and short (<30 days) deployments on soldiers, and assess correlations with current biological and psychological measures of stress.
DoD-133	Pamela Dalton	Monell Chemical Senses Center	Odors, Deployment Stress, and Health: A Conditioning Analysis of Gulf War Syndrome	Investigate the ability of odors to become associated with stressors and to elicit conditioned stress responses and health symptoms in humans. Will also determine factors for development, persistence and extinction of the response, and develop methods to prevent formation of responses where stressors and odors are likely to occur together.
DoD-140	Megan Ryan	Naval Health Research Center	US Department of Defense Surveillance for Neoplasms in Infancy	Create a pediatric cancer registry to ascertain cases of cancer among children of military personnel, and compare cancer rates between children of Gulf War veterans and non-deployed veterans.
DoD-141	Carolyn Breda	Vanderbilt University	Physical, Mental, Social, and Family Health Outcomes of Gulf War Veterans	Evaluate effects of the Gulf War deployment on physical, mental, social, and family problems over time. This study uses state-of-the-art multivariate analyses with hierarchical and growth curve models to reanalyze existing data collected for a different purpose.

IV.A.2. Clinical Trial of Cognitive-Behavioral Treatment for PTSD in Women

VA and DoD have jointly funded a randomized clinical trial of two types of cognitive-behavioral therapy of PTSD in women (Project VA-74/DoD-125). 384 female active-duty personnel and veterans will receive treatment at Walter Reed Army Medical Center and at 11 VA sites. PTSD is a specific health concern in women that leads to substantial psychosocial and functional disability. Approximately 8 to 10% of active-duty and veteran women suffer from PTSD. This study targets women who have been traumatized during military service. Most often, military trauma in women involves sexual assault, but other sources are physical assault, accidents, disasters, and war-zone exposure, including medical assignments that involve exposure to seriously injured personnel.

The primary hypothesis is that Prolonged Exposure will be more effective than Present-Centered Therapy for the treatment of PTSD due to military-related trauma in women. Prolonged Exposure consists of 10 weekly treatment sessions that include education about and exposure to the memories of the trauma in which the patient was involved. The patient is guided through a vivid remembering of the traumatic event repeatedly, until the patient's emotional response decreases through habituation. Present-Centered Therapy consists of 10 weekly individual treatment sessions that focus on current life problems and provide emotional support for the patient.

Severity of PTSD will be measured with the Clinician Administered PTSD Scale (CAPS), which is considered the gold standard for assessment of PTSD. Severity of symptoms will be assessed at intake, and at follow-up, which will be at 3 and 6 months post-treatment. In addition, depression and anxiety symptoms will be followed over time, using the Beck Depression Inventory and the State-Trait Anxiety Inventory. This project started enrollment of patients in January 2002. The project period is four years, at a cost of $5.0 million.

IV.A.3. Two Projects on Effective Risk Communication Methods for Active-Duty Service Personnel and Veterans

In March 2001, CDC published a Request for Proposals, entitled "Strategies for Improving Health Risk Communication Related to Military Deployments among Military Personnel, Veterans, Their Family Members, and Their Health Care Providers." The goal is the development, implementation, and evaluation of risk communication strategies, in order to provide more timely, understandable, and effective communications. The need to improve these methods has been highlighted in reports by the Presidential Advisory Committee on Gulf War Veterans' Illnesses, the Presidential Review Directive 5, and the Institute of Medicine. (PAC, 1996b; NSTC, 1998; IOM, 1999)

After peer review, CDC funded two projects in September 2001, each of which will be funded for approximately $400,000 per year for up to three years. One project at Rutgers University (Project HHS-9) is entitled "Improving Health Risk Communications to Prevent Unexplained Illnesses Related to Military Deployments." This study will focus on how military personnel think about deployment-related health risks, in terms of knowledge, attitudes, and beliefs. The three-phase study will include: a survey of Gulf War veterans' beliefs about unexplained illnesses; a survey of mental models of active-duty personnel about illnesses; and development and evaluation of risk communication documents related to specific deployment-related risks.

The second project, which is located at Walter Reed Army Medical Center (Project HHS-10), is entitled "Health-e VOICE: Optimized Implementation of a Stepped Clinical Risk Communications Guideline." This study will develop and evaluate an interactive, web-based distance learning tool, targeted to DoD health care providers. Its intention is to facilitate provider/service member communication about deployment-related health concerns. The basis for the web site will be the Clinical Practice Guidelines for Post-Deployment Evaluation and Management, which DoD implemented in March 2002. These Guidelines address four types of patients: asymptomatic/ deployment health concerns; recently deployed/seeking care; recent onset of multiple unexplained symptoms; and persistent, disabling, multiple unexplained symptoms. The web-based tool will be evaluated for usability and provider/service member acceptability. In addition, provider mental models will be evaluated, regarding post-deployment health concerns. The impact of the tool on providers' knowledge, attitudes, and behaviors will be assessed.

B. 2001 UPDATE OF KEY RESEARCH PROJECTS AND INITIATIVES

Three research initiatives are described in this section:

- an Institute of Medicine report;
- the Gulf War Veterans Medical Library Web Site, funded by CDC and DoD; and
- the 2001 Plenary Conference of the Military and Veterans Health Coordinating Board.

IV.B.1. Institute of Medicine Study on Identification of Effective Treatments of Illnesses in Gulf War Veterans (IOM, 2001), and VA and DoD Plans for Implementation of IOM Recommendations

Public Law 105-368, which was enacted on November 11, 1998, was entitled the "Veterans Programs Enhancement Act of 1998." It mandated that the VA contract with the NAS to review the available scientific data to:

- "Assess whether a methodology could be used by the VA for determining the efficacy of treatments furnished to, and health outcomes (including functional status) of, Persian Gulf War veterans who have been treated for illnesses; and
- Identify, to the extent feasible, with respect to each undiagnosed illness prevalent among such veterans and for any other chronic illness that the NAS determines to warrant such review, empirically valid models of treatment for such illness which employ successful treatment modalities for populations with similar symptoms."

In 1999, the VA requested the Institute of Medicine to perform an 18-month study to identify effective treatments for health problems in Gulf War veterans. (IOM, 2001) The committee's charge was threefold, as follows:

1. Identify and describe approaches for assessing treatment effectiveness.
2. Identify illnesses and conditions common among Gulf War veterans, including medically unexplained symptoms, using data obtained from the VA and DoD Gulf War registries, as well as information in published articles.
3. Identify validated models of treatment for these identified conditions and illnesses; or identify new approaches, theories, or research on the management of patients with these conditions, if validated treatment models are not available.

The committee's charge was not to examine exposures or causes of health problems, but to identify effective treatments for health problems that exist.

The IOM committee held its first meeting in February 2000, and it held a total of 5 meetings through January 2001. A public meeting was held in August 2000 to gather information from veterans, veterans' service organizations, scientists, health care providers, and congressional staff. Its report was published in July 2001, entitled *Gulf War Veterans: Treating Symptoms and Syndromes*. (IOM, 2001)

IOM concluded that "Most Gulf War veterans have not experienced the troubling and sometimes debilitating symptoms that plague some" veterans. IOM also concluded "For those Gulf War veterans who have been evaluated in the VA and DoD Gulf War registries (about 120,000 individuals), about 80% have received readily identifiable diagnoses that explain their symptoms. For 20% of registry participants, however, no diagnosis has been found."

IOM stated that difficult-to-diagnose symptoms experienced by some Gulf War veterans have a large overlap with the following seven diagnoses: chronic fatigue syndrome, depression, fibromyalgia, headache, irritable bowel syndrome, panic disorder, and PTSD. The committee reviewed clinical practice guidelines, major literature reviews, and published studies of treatments for these conditions. In its evaluation, the committee chose to recommend as effective only those treatments with demonstrated efficacy using the highest level of evidence-the randomized controlled trial. There is a detailed discussion of each of these conditions, including diagnostic criteria; evaluation of therapies describing benefits, harms, and comments; practice issues; and recommendations. IOM concluded that available studies of proven therapies for persons with these disorders are a valuable resource for deriving effective treatments of undiagnosed illnesses.

A major focus of the report was the evaluation of proven treatments for these recognized diagnoses, and recommendations for improving health care for patients with these disorders. For example, IOM recommended two therapies for chronic fatigue syndrome, because they were likely to be beneficial-cognitive behavior therapy and exercise therapy. VA and DoD recently completed a randomized clinical trial of Gulf War veterans with symptoms similar to chronic fatigue syndrome (Project VA-62/DoD-115). Cognitive behavior therapy and aerobic exercise were the two treatments that were compared with usual care. The results of this large trial will be published in 2002.

VA has already implemented many of the IOM recommendations that focused on improved clinical care for veterans. For example, VA has developed clinical practice guidelines for chronic fatigue syndrome, fibromyalgia, and depression. IOM also made three research recommendations, as follows.

IOM Research Recommendations and VA and DoD Plans for Implementation

1. IOM recommends that VA design future studies of treatment effectiveness that include outcomes research and effectiveness randomized clinical trials.

- VA and DoD have already undertaken several initiatives that address this recommendation. VA and DoD have jointly funded 3 large randomized clinical trials in Gulf War veterans. These are the Exercise Behavioral Therapy Trial (EBT) (Project VA-62/DoD-115); the Antibiotic Treatment Trial (ABT) (Project VA-55/DoD-119); and the PTSD treatment trial in women (Project VA-74/DoD-125). Patients who were eligible to participate in the EBT and ABT had undiagnosed, disabling symptoms that resembled chronic fatigue syndrome and fibromyalgia. The EBT and ABT have recently been completed and will be published in 2002. The PTSD treatment trial began in 2001, and it is described in Section IV.A.2. of this report.

2. IOM recommends that those conducting ongoing cohort studies of veterans' health (e.g., the VA National Health Survey, the Iowa follow-up study on Gulf War veterans, and the Millennium Cohort Study being implemented by DoD) include collection of data on treatments and health-related quality of life.

- VA and DoD have already undertaken several initiatives that address this recommendation. Several ongoing and completed studies have included data on treatments and health-related quality of life. For example, in 2001, four studies reported on health-related quality of life among Gulf War veterans in Boston, Massachusetts; Portland, Oregon; Cleveland and Cincinnati, Ohio; and Great Britain. (Proctor, et al., 2001a; Bourdette, et al., 2001; Baker, et al., 2001; Chalder, et al., 2001) Each of these studies is summarized in Section II of this report. In addition, each of the three large cohort studies cited by IOM includes data on treatments and health-related quality of life.

3. IOM recommends that current VA and DoD Gulf War registries be used as one way to identify patient samples and serve as a sampling frame for future treatment effectiveness studies.

- VA and DoD have already undertaken several initiatives that address this recommendation. For example, VA funded five treatment demonstration projects in 1998. The primary sources of patients in these studies were the Gulf War registries at eight VA Medical Centers. A key goal was to test new and innovative clinical approaches for treating Gulf War veterans who have medically unexplained symptoms. Some of the five projects also emphasized treatment of the seven diagnoses in the IOM report, such as PTSD and depression. These projects were completed in 2000, and the final progress reports are available at www.va.gov/health/environ/persgulf.htm. In 2001, preliminary results from two of the studies were published in the peer-reviewed medical literature. (Baker, et al., 2001; Richardson, et al., 2001) These two studies are summarized in Section II of this report. Also, DoD has evaluated the effectiveness of treatment of patients with disabling, chronic symptoms in the DoD Gulf War registry. (Engel, et al., 2000a)

IV.B.2. Gulf War Veterans Medical Library Web Site

In 2001, CDC made funding available to develop a web site that was designed to provide

accessibility to information on the health effects of deployment to the Gulf War. CDC collaborated with the DoD Office of the Special Assistant for Gulf War Illnesses (OSAGWI), because of its experience in building the GulfLINK web site since 1997. GulfLINK was designed to provide information on numerous issues of interest to Gulf War veterans; however, it has not focused on medical research. In addition, OSAGWI has expertise in building complex Oracle databases.

The working title of the new web site is Medsearch. Its primary target audience is veterans; therefore, there has been an emphasis on making the site's functions user-friendly, and on the use of plain English, whenever possible. As the overall framework of the web site was being constructed, the developers decided that the *1999 Annual Report to Congress* should be used as the starting point and model for the overall web structure. (PGVCB, 2001) This report was chosen because it was comprehensive in scope, and because of the utility of its classification system for various types of medical studies. A glossary of medical terms is being developed to improve comprehension.

The web site will include summaries of all ongoing Federally-funded research projects on illnesses in Gulf War veterans. The web site will be updated frequently to ensure that it contains the most recent and complete information available. Some research projects have their own web sites, such as the Millennium Cohort Study (Project DoD-143). In such cases, Medsearch will provide hyperlinks to the project web sites. Available abstracts of published articles will be included, which have been hyperlinked from PubMed. PubMed is the web site for Index Medicus, which is maintained and updated by the National Library of Medicine. A special focus will be to obtain and computerize government reports that might be difficult for the public to identify or obtain. Examples include reports by the Senate Veterans' Affairs Committee and the Presidential Special Oversight Board. (SVAC, 1998; PSOB, 2000)

As of February 2002, the web site developers were testing the web site with focus groups of Gulf War veterans and active-duty service members. To date, the comprehensive scope and the ease of use of the web site have been reviewed favorably. The web site will be publicly released by mid-2002.

IV.B.3. 2001 Military and Veterans Health Coordinating Board Plenary Session

The MVHCB organized and hosted a conference, entitled "Second Annual Plenary Session." It was held on December 10-12, 2001, in Rockville, Maryland. The purposes of the meeting were to provide an update on issues related to the health consequences of deployment, and to facilitate coordination and collaboration among members of the three Services and among DoD, VA, and HHS. The presentations were planned to directly address progress made related to recommendations contained in Presidential Review Directive 5, and related to requirements of the DoD Force Health Protection Program. (NSTC, 1998; Joint Chiefs of Staff, 1999) This was the second such Plenary Session. A smaller conference had been held in September 2000 at Andrews Air Force Base.

Over three days, the sessions were organized into several major topics, as follows:

- Results of research on illnesses in Gulf War veterans
- Ongoing research initiatives related to Force Health Protection
- Developing and maintaining a fit and healthy force through a continuum of care
- Functional approaches to collecting and managing data on personnel and exposures
- Systematic approaches to evaluating and managing battle and non-battle related risks
- DoD/VA life cycle health surveillance system capabilities
- Development of health risk communication strategies and skills

Approximately 150 scientists, clinicians, government officials, and active-duty service members attended this conference, including medical representatives of the British and Canadian armed forces. The detailed agenda for this conference is included in Appendix B of this *Annual Report to Congress*.

V. RESEARCH MANAGEMENT

A. Overview

Research on Gulf War veterans' illnesses is a complex undertaking, involving a number of different approaches. The Federal research effort on this problem involves scientists in Federal, academic, and private institutions, both in the United States and abroad, conducting research sponsored by VA, DoD, and HHS. Each of these Departments has distinct, complementary capabilities and capacities for conducting and sponsoring research on Gulf War veterans' health issues. Also, each Department has its own appropriation for extramural and intramural general biomedical research programs.

The biomedical research programs in VA, DoD, and HHS have well-established management structures for science policy formulation and the solicitation, scientific peer review, and funding of both extramural and intramural programs. Each Department's research management hierarchy for Gulf War veterans' illnesses research has been linked through an overall coordinated effort carried out by the Research Working Group (RWG) of the Military and Veterans Health Coordinating Board (MVHCB). As an operational policy, the RWG works through the management authority that each Department maintains over its intramural scientists, its scientific program managers who are responsible for extramural research, and its budgets. However, the RWG has no budget authority itself, therefore, all funds for research flow through the funding agency or Department.

VA and DoD, with the encouragement of Congress, have established centers for research on deployment health. The centers' activities are fully coordinated and involve collaboration across agencies. These centers have undertaken research addressing such topics as joint clinical treatment trials, post-deployment clinical practice guidelines, and longitudinal studies of health outcomes related to future deployments.

B. Oversight of Research

Each Department engaged in research on Gulf War veterans' illnesses endorses the need for both prospective and retrospective scientific peer review of research. Review and oversight of research have been important, because of the urgency of the health concerns of Gulf War veterans and their families, and the diverse nature of the reported illnesses. VA, DoD, HHS, and the Executive Office of the President have established multiple oversight mechanisms to capture the full spectrum of the overall effort. Some oversight mechanisms are broad-based, encompassing all research issues, while others are more focused on individual research projects and programs.

Four of the most important oversight activities are briefly discussed below. Although each has had a broad mandate that has encompassed virtually all issues related to Gulf War veterans' illnesses, the discussion below will focus on their research oversight activities, findings, and recommendations.

1. Institute of Medicine/Medical Follow-up Agency: *Health Consequences of Service During the Persian Gulf War*

As directed by Public Law 102-585, VA and DoD jointly entered into a contract with the Medical Follow-Up Agency (MFUA) of the Institute of Medicine, National Academy of Sciences. The three-year IOM contract started on September 30, 1993. The IOM was mandated to review existing scientific, medical and other information on the health consequences of military service during the Gulf War. The IOM was also mandated to write a report that focused on the following:

- an assessment of the effectiveness of actions taken by the VA and DoD to collect and maintain information that is potentially useful for assessing the health consequences of military service in the Gulf War;
- recommendations on means of improving the collection and maintenance of such information; and
- recommendations on whether there is sound scientific basis for an epidemiological study or studies on the health consequences of service in the Gulf War, and the nature of such study or studies.

On January 4, 1995, the IOM issued a report, entitled *Health Consequences of Service During the Persian Gulf War: Initial Findings and Recommendations for Action* (IOM, 1995). In general, the IOM panel endorsed previous findings of the Defense Science Board (DSB, 1994) and a National Institutes of Health

Technology Assessment Workshop (NIH, 1994) that no single disease entity could be identified for the health complaints expressed by Gulf War veterans. The panel also strongly emphasized the importance of population-based studies, several of which are ongoing.

The final IOM report of September 1996 stands as a separate document from its initial January 1995 report. It is entitled *Health Consequences of Service During the Persian Gulf War: Recommendations for Research and Information Systems*. (IOM, 1996) The IOM panel stated that it could find no scientific evidence to date demonstrating adverse health consequences associated with service in the Gulf War beyond the few documented cases of leishmaniasis, combat-related or injury-related mortality or morbidity, and increased risk of psychiatric sequelae of deployment. The panel went on to state that there is a strong likelihood that no single hypothesis could account for all illnesses reported by Gulf War veterans, whether or not they resulted from service in the Gulf War. Finally, the panel observed that after previous wars and conflicts, a proportion of military service personnel and veterans have had medical complaints of varying degrees of severity that are not explainable based on identifiable health hazards or physical illnesses. This observation echoes studies by Hyams, et al. (1996) and Jones, et al. (2002), which demonstrated this phenomenon back at least to the Civil War.

The IOM panel made the following research recommendations:

- Determine factors for possible response differences among active and non-active duty service members.
- Conduct mortality studies on Gulf War veterans out to at least 30 years.
- Determine the reason for excess deaths by external causes among Gulf War and other veterans.
- Continue and extend the Defense Medical Epidemiological Database.
- Refine geographical information systems (GIS) for troop locations and plan for future conflicts.
- Conduct reviews of the Total Exposure Assessment Methodology used to predict pollutant exposure in the Gulf War.
- Study gender issues when assessing health effects of deployment.
- Conduct studies on the consequences of assigning men and women to serve together.
- Complete and publish the Naval Health Research Center epidemiology studies.
- Complete and publish the VA National Survey of Persian Gulf Veterans.
- Complete evaluation of predictors of VA registry enrollment.
- Strengthen the epidemiological capabilities of the armed forces.
- Submit all research (intra- and extramural) for peer review publication in a timely manner.

Each of these IOM recommendations has been implemented by VA, DoD, or HHS, as appropriate. The progress, to date, is summarized in Section VI Research Priorities.

In accordance with P.L. 102-585, the agreement with IOM has been extended for the general purposes of providing core epidemiological support for research on military and veteran populations. This support provides a valuable infrastructure to carry out epidemiological research on Gulf War veterans' illnesses. The Medical Follow-up Agency of the IOM has conducted a number of related projects (DoD-69, DoD-93, DoD-116/VA-63, and DoD-117).

2. Executive Office of the President: Presidential Advisory Committee on Gulf War Veterans' Illnesses (PAC)

The President established the PAC by Executive Order on May 26, 1995. Between August 1995 and January 1997, the Committee met a total of 23 times either as a full Committee or in subcommittees. The 12 member committee was composed of scientists, health care professionals, veterans, and policy experts. The Committee was charged with reviewing and providing recommendations on the full range of activities relating to the government's response to Gulf War veterans' illnesses. In addition the Committee evaluated the available data on the nature of Gulf War veterans' illnesses and on potential health effects related to Gulf War risk factors.

The Committee released an interim report in February 1996 (PAC, 1996a). Although the Interim Report stated that VA, DoD, and HHS research programs were generally well-designed and should lead to meaningful answers to issues

concerning Gulf War veterans-related health issues, it also had several recommendations. The Committee's recommendations covered issues such as peer review, coordination of agency research activities, the use of public advisory committees, and the availability of information on troop exposures. The Committee made no findings about specific illnesses or risk factors in the Interim Report. In response to the Interim Report, the Departments developed a coordinated plan of action that responded to the Advisory Committee's interim recommendations.

The Final Report of the Committee was released in December 1996 (PAC, 1996b). The PAC came to the following conclusions:

- Many veterans have illnesses likely to be connected to service in the Gulf War.
- Current scientific evidence does not support a causal link between the symptoms and illnesses reported today by Gulf War veterans and exposures while in the Gulf to:

  Pesticides
  Chemical warfare agents
  Biological warfare agents
  Vaccines
  Pyridostigmine bromide
  Infectious diseases
  Depleted uranium
  Oil well fires and smoke
  Petroleum products

The Final Report also concluded that stress (known to affect the brain, immune system, cardiovascular system, and various hormonal responses) is likely to be an important contributing factor to Gulf War veterans' illnesses.

The Final Report made the following research recommendations:

- Require any new large-scale epidemiologic studies to have scientific and public advisory committees.
- Develop more accurate and reliable troop locator systems.
- Plan and conduct further research on low-level exposure to organophosphate chemical warfare nerve agents.
- Monitor Gulf War veterans for increased rates of cancer through mortality studies.
- Conduct research on the health status of individuals with embedded depleted uranium fragments.
- Collect and archive serum samples from U.S. service personnel when feasible.
- Conduct basic and clinical research on the physiologic effects of stress and stress-related disorders.
- The Research Working Group should consult more thoroughly with other Federal agencies.

Each of these PAC recommendations has been implemented by VA, DoD, or HHS, as appropriate. The progress, to date, is summarized in Section VI Research Priorities.

Because of concern over the adequacy of investigations into reports of possible chemical and biological warfare exposure incidents during the Gulf War, and because of a need to follow up on recommendations from the Committee's Final Report, the President extended the Committee through October 1997. At that time the PAC issued a Special Report (PAC, 1997). In the Special Report, the Committee did not alter its findings and conclusions with respect to potential causes of Gulf War veterans' illnesses. The Special Report did not contain any specific recommendations for research.

With respect to Federally funded research on Gulf War veterans' illnesses, the PAC concluded that the Government has been adequately and appropriately responding to its recommendations. (PAC, 1997) The PAC particularly commended the Government for its new initiatives targeted on health effects of low-level exposure to chemical warfare (CW) agents. As the PAC noted in its Final Report, "the amount of data from either human or animal research on low-level exposures [to CW agents] is minimal." However, in its Special Report, the PAC concluded that planned research on the health effects of low-level exposure might address any uncertainties and inconclusiveness identified in the Final Report.

The PAC approved of the government's targeted solicitations for research and the process used to make such awards. (PAC, 1997) However, the Committee expressed reservations about a perceived deficiency in processes for funding some research projects related to Gulf War veterans' illnesses. The Committee noted that "competition and external peer review of

research proposals are essential to guarantee scientific merit, relevance, and level of priority generally." The Committee acknowledged that benefit could accrue from small-scale, short-term funding on a sole source basis for pilot projects or to address narrow scientific questions. The Committee stated, though, that such approaches should be rare and that protocols still should be peer reviewed prior to funding, limited in the amount of funds released, and not subject to renewal without competition.

The RWG of the MVHCB will continue to endorse peer review and competition as the means of obtaining the best research products.

3. Senate Veterans' Affairs Committee: ***Report of the Special Investigation Unit on Gulf War Illnesses***

The Senate Veterans' Affairs Committee undertook a year-long investigation in 1997, and published a comprehensive report in 1998. (SVAC, 1998) The Special Investigative Unit (SIU) examined the policies and actions of the U.S. government that have had an impact on the current health of Gulf War veterans.

Specific areas of concern were encompassed: the DoD's plans and policies; the intelligence community's role; health risks encountered by U.S. troops during the war; record keeping before, during, and after it; and the VA's accountability to and responsibilities for Gulf War veterans.

The major conclusions of the SVAC related to research were:

- While there does not appear to be any single "Gulf War Syndrome," there is a constellation of symptoms and illnesses whose cause or causes eludes explanation at this time.
- There is a great need to monitor those veterans who are ill, or who may become ill in the future, to assess whether they are getting better or worse and to define better the long-term effects they may experience.
- There is insufficient evidence to prove or disprove that there was an actual low-level exposure of any troops to chemical weapon nerve agents, or that any of the health effects some veterans are experiencing were caused by such exposure.
- In the inherently difficult area of military health, research that is conducted before illnesses occur, not after the fact, can help to assure prompt, effective medical treatment; to prevent adverse health effects in the first place; and to provide clear information to veterans who may be adversely affected by such exposures.

The SVAC made the following research recommendations:

- DoD should fund research into the health effects of depleted uranium exposure.
- DoD should establish a program to improve the capacity for rapid and early detection of exposures that may affect troop health during and after deployments; for example, to develop technology to rapidly screen persons exposed to a wide range of chemical toxins, including chemical warfare agents.
- DoD and VA should monitor the treatment provided to ill Gulf War veterans on an ongoing basis, especially those with unexplained illnesses, to determine whether those veterans are getting better or worse over time.
- DoD and VA should implement methods to monitor the health status of Gulf War veterans over time to provide early detection of future illnesses that may emerge years later, such as higher rates of cancer.
- DoD and VA should establish a birth defects registry for military service members to gather statistics on possible reproductive health effects stemming from battlefield exposures.
- DoD and VA should evaluate treatment protocols that have been useful for persons in the general population who suffer from illnesses similar to Gulf War veterans' unexplained illnesses, and they should fund appropriate clinical programs and research in this area.
- DoD and VA should fund Gulf War health research only through an impartial, scientific peer review process, except in the case of the most serious circumstances.

Each of the SVAC recommendations has been implemented by DoD and VA. The progress, to date, is summarized below, in Section VI Research Priorities.

4. Presidential Special Oversight Board: ***Final Report of Special Oversight Board for Department of Defense Investigations of Gulf War Chemical and Biological Incidents***

The Presidential Special Oversight Board (PSOB) was established in June 1998 in response to a recommendation of the Presidential Advisory Committee on Gulf War Veterans' Illnesses. (PAC, 1997) The *Final Report* of the PSOB was published on December 20, 2000. (PSOB, 2000)

The PSOB charter called for it to "provide advice and recommendations [and oversight] . . . of DoD investigations into possible detections of, and exposures to, chemical or biological warfare agents and environmental and other factors that may have contributed to Gulf War Illnesses . . . [and to provide an] overall evaluation of DoD's plan for and progress toward the implementation of the Presidential Advisory Committee's recommendations contained in its Special Report." (PSOB, 2000)

There were a limited number of research conclusions and recommendations in this report, which were scattered in the report, rather than clustered in a summary. (PSOB, 2000) Most of the report was not directly related to research, since most of the report focused on an evaluation of the work of the DoD Office of the Special Assistant for Gulf War Illnesses (OSAGWI).

The major conclusions related to research in the PSOB *Final Report* were:

- "After every deployment of troops for war, similar symptoms have occurred in returning service personnel. This 'post-war syndrome' has been attributed to the stresses of deployment. It has been described in various ways in every war since the Civil War. . . The Board concludes that it is highly likely that a proportion of Gulf War veterans suffering from the symptoms of undiagnosed illnesses fall into the generalized category of 'post-war syndrome' or post deployment illness. As with all previous wars, stressful deployments to a combat zone can create significant medical problems for returning troops." (pages 44-45)

- "Mental disorders clearly affect military readiness. These factors are the second leading cause of hospitalization, the leading cause of inpatient bed days, and the leading medical cause of attrition from the military service. Mental disorders are also the most important cause of medical and occupational morbidity among active duty US military personnel." (page 72)

- "The only known potential exposure of US personnel to chemical warfare agents remains the accidental low-level release of nerve agents during demolition operations at Khamisiyah, Iraq, in March 1991." (page ii)

- "Based on the current body of evidence in the medical literature on studies of humans accidentally exposed to organophosphate nerve agents and on controlled animal exposures to organophosphate nerve agents at levels causing no acute signs or symptoms, low-level exposures do not produce chronic illnesses. However, gaps exist in the scientific literature regarding the potential long-term health consequences of exposure to low concentrations of nerve agents that are initially asymptomatic." (pages 48-49)

- "The Board concludes that DU [depleted uranium] is unlikely to be the cause of either the unexplained illnesses among Gulf War veterans or the diagnosed illnesses found during CCEP and VA Registry evaluations." (page 51)

- "The Board concurs with both the RAND study on PB [pyridostigmine bromide] and the Institute of Medicine analysis that 'available evidence is of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of an association [of PB use with adverse health effects] in humans.' " (page 55)

In its *Final Report*, the PSOB made the following research recommendations:

- "The Board concludes that stress is likely a primary cause of illness in at least some Gulf War veterans; it is a likely secondary factor in potentiating other causes of undiagnosed illnesses among some Gulf War veterans. . . This issue requires continued research. The Board commends DoD for recognizing the role of stress in

deployment and in combat and for developing and implementing programs to address this issue." (page iv)

- "The Board recommends that OSAGWI and the MVHCB closely monitor the development and resourcing of DoD's research on the health effects of low-level CWA [chemical warfare agent] exposures and make recommendations as appropriate to ensure continued progress in this area." (page vii)

- "The Board strongly believes that efforts to fund non-peer reviewed research projects do not serve the best interest of the nation or of its Gulf War veterans. Researchers and clinicians who advocate 'alternative' diagnostic and treatment methods, as well as those proposing more conventional approaches, should be encouraged to respond to Requests for Proposal and Broad Agency Announcements with well-constructed proposals capable of passing vigorous and independent peer review." (page viii)

- "The Board believes that DoD should fully support the Millennium Cohort Study and that the service members selected to participate in the program should cooperate fully. This twenty-year research project will significantly enhance the Federal Government's and the medical community's understanding of the long-term health consequences of military service and facilitate improved clinical care and force health protection for members of the Armed Forces." (page ix)

- "The Board concurs with the Institute of Medicine recommendations for: '1) additional studies in experimental animals to investigate the specific effects of DU; and 2) long-term follow-up of veterans exposed [and potentially exposed] to DU, including . . . [those] involved in clean-up operations or radiation control units.' " (page 51)

- "Further study is clearly needed in this area [pyridostigmine bromide], since PB remains the only viable prophylactic agent for soman exposure, and DoD intends to continue its use in future conflicts." (page 55)

- "PRD-5 recommended DoD possess the capability to collect and assess data associated with anticipated exposures during deployments and to respond to newly identified threats. . . The Board believes that the complexity of accurate assessment tools and epidemiological standards have inhibited progress in this area of environmental health research. The Board recommends that DoD develop and implement a system for applied toxicological research based on prioritized lists of environmental and occupational substances, as suggested in PRD-5." (page 74)

Each of the PSOB recommendations has been implemented by DoD and VA. The progress, to date, is summarized below, in Section VI Research Priorities.

5. Other Oversight

In addition to the broad oversight that has been provided by the four committees cited above, there are several standing and special committees responsible for oversight on individual research projects and programs. Additionally, valuable review and oversight has been provided by the House Committee on Veterans' Affairs, the House Committee on Government Reform, and the General Accounting Office.

C. Research Coordination

In 1993, VA, DoD, and HHS recognized the importance of a coordinated approach to research on Gulf War veterans' illnesses and formed the "Persian Gulf Interagency Research Coordinating Council." In January 1994, the Secretaries of VA, DoD, and HHS formed the Persian Gulf Veterans Coordinating Board. The Research Coordinating Council became the Research Working Group (RWG), operating under the auspices of the Coordinating Board. In 2000, the mission of the RWG broadened to include issues of Force Health Protection, as the PGVCB transitioned to become the MVHCB. (PGVCB, 2001) Membership on the RWG consists of senior research scientists and clinical managers from VA, DoD, and HHS.

The RWG includes various subcommittees that have been in existence over the past several years. A subcommittee for planning conferences has been responsible for organizing five

meetings of Federally funded researchers. These meetings have provided an opportunity for researchers to gather and share recent research results and to discuss research problems of mutual interest. The 2001 conference was an open meeting allowing for extensive interactions among researchers, clinicians, veterans, and other members of the public.

The RWG reevaluated its general functions in September 2000, when the PGVCB transitioned to the MVHCB. The consensus statement on general functions is:

- The Research Working Group will provide coordination of the interagency research strategy, related to deployment health and health risk communication initiatives, affecting military personnel, veterans, and their families. It will:

1. Assess the state and direction of research to identify new ideas or new research approaches, to identify gaps in scientific knowledge, and to make recommendations regarding research priorities.

2. Promote and encourage appropriate scientific review of research sponsored by the Federal government.

3. Make recommendations concerning appropriate actions and responses to research findings.

4. Provide a forum for information exchange about research initiatives and priorities among the Departments of Defense, Veterans Affairs, and Health and Human Services, and the national and international research community.

Programmatic Review of Extramural Research Proposals

An important function of the RWG is programmatic review of research proposals, that have been competitively reviewed, to provide recommendations to funding agencies. Research on illnesses in Gulf War veterans includes intramural projects performed by scientists who are employed by the Federal government, and extramural projects performed by scientists who are employed by universities, private laboratories, or other independent organizations. The RWG works collectively with VA, DoD, and HHS to establish research needs and identify agency-specific funding mechanisms to support that research. For a specific research funding activity, the responsible funding agency works in coordination with the RWG to develop a targeted solicitation for research.

Proposals that are submitted to the funding agency in response to a solicitation are scientifically peer reviewed using agency-specific peer review programs. For example, the Department of the Army in DoD uses a contract with the American Institute of Biological Sciences. The AIBS is chartered by the National Academy of Sciences to conduct peer review for Federal agencies.

Abstracts of peer-reviewed proposals, summaries of the reviews of the peer reviewers, and the scientific merit scores assigned by the peer reviewers are provided to a subcommittee of the RWG charged with providing secondary review of proposals for relevance. Relevance determinations are guided by interagency programmatic needs articulated through the RWG process and reflected in the *Working Plan for Research on Persian Gulf Veterans' Illnesses* (1996b). In its secondary review, the RWG may re-rank proposals based on relevance, but it will not recommend funding for any non-meritorious proposal, regardless of relevance or availability of funds. The RWG has no budget authority; therefore all final funding decisions about research are made by the individual agencies. The RWG will continue to work diligently to foster the highest standards of competition and peer review for all research on Gulf War veterans' illnesses.

Notable among the activities of the RWG are:

- Development, production, and dissemination of the 1995 *A Working Plan for Research on Persian Gulf Veterans' Illness* (PGVCB, 1995b), and its 1996 revision (PGVCB, 1996b).

- Production and dissemination of *Annual Reports to Congress* for 1994 through 2001 on results, status, and priorities of Federal research activities. (PGVCB, 1995a; 1996a; 1997; 1998a; 1999a; 2001; MVHCB, 2001a; 2002)

- Secondary programmatic review of research proposals that have been competitively reviewed by funding agencies.

- Organization of five conferences of Federally funded researchers, including publication of three Proceedings (PGVCB, 1998b; 1999b; MVHCB, 2001b).

- Coordination and oversight of implementation of relevant recommendations of the Institute of Medicine, Presidential Advisory Committee, Senate Veterans Affairs' Committee, the Presidential Review Directive 5, and the Presidential Special Oversight Board (IOM, 1995, 1996; PAC, 1996a, 1996b, 1997; SVAC, 1998; NSTC, 1998; PSOB, 2000).

- Three national treatment trials (exercise/ behavior trial, antibiotic treatment trial, and PTSD treatment trial in women).

- Organization of an international symposium in 1997, in conjunction with the Society of Toxicology on the health effects of low-level exposure to chemical warfare nerve agents.

- Development of a strategy for research on the health effects of exposure to low-levels of chemical warfare nerve agents. (PGVCB, 1998a)

- Follow-up investigation of preliminary reports of positive experimental serological tests for leishmaniasis in Gulf War veterans.

VI. RESEARCH PRIORITIES

The Research Working Group has identified three sets of research priorities in 1995, 1996, and 1998. (PGVCB, 1995b; 1996b; 1999a) Substantial progress has been made on each of these priorities, which is summarized here.

A. RESEARCH PRIORITIES FOR 1995

In 1995, the scope and magnitude of the research activities required implementation of a comprehensive plan. This resulted in the publication of *A Working Plan for Research on Persian Gulf Veterans' Illnesses* on August 5, 1995. (PGVCB, 1995b) The *Working Plan* was coordinated by the Department of Veterans Affairs (VA), in conjunction with the PGVCB. The plan mapped out the course to pursue the following overarching goals:

- Establish the nature and prevalence of symptoms, diagnosable illnesses, and unexplained conditions among Persian Gulf veterans in comparison to appropriate control groups.

- Identify the possible risk factors for any illnesses, beyond those expected to occur, among Persian Gulf veterans.

- Identify appropriate diagnostic tools, treatment methods, and prevention strategies for any excess illness conditions found among Persian Gulf veterans.

A key component of the 1995 *Working Plan* was an assessment of current knowledge and research on Gulf War veterans' illnesses. This assessment led to the identification of 19 research questions, which are included below, in the section on research priorities for 1996.

This assessment also led to the identification of the following issues for which significant gaps in knowledge existed in 1995:

1. Information on the prevalence of symptoms, illnesses, and/or diseases within other coalition forces.
2. Information on the prevalence of symptoms, illnesses, and/or diseases within indigenous populations within the Persian Gulf area including Saudi Arabia and Kuwait.
3. Information on the prevalence of adverse reproductive outcomes among Persian Gulf veterans and their spouses.
4. Simple and sensitive tests for *L. tropica* infection that could lead to quantification of the prevalence of *L. tropica* infection among Persian Gulf veterans.
5. Information on the long-term, cause-specific mortality among Persian Gulf veterans.

Each of these research issues has been addressed since 1995, as follows:

1. The US government has coordinated its research effort with the UK and Canada, as coalition partners in the Gulf War. The UK fielded the second largest force during the Gulf War, including 53,000 service members. The US DoD has funded epidemiological research in the UK, which has compared the health of British Gulf War veterans, Bosnia veterans, and non-deployed veterans (projects DoD-39, DoD-106, and DoD-142). The results of the first phase of the British investigation have been published. (Unwin, et al., 1999; Ismail, et al., 1999; Hotopf, et al., 2000; Ismail, et al., 2000; Chalder, et al., 2001; Reid, et al., 2001) In addition, a second large epidemiological study of a separate cohort of British Gulf War veterans was recently published. (Cherry, et al., 2001a; Cherry, et al., 2001b) The Canadian government has published a comprehensive study of the health of Canadian Gulf War veterans, compared to non-deployed veterans. (Goss Gilroy, 1998) Denmark also participated in the Gulf War as a coalition partner, primarily in the postwar period after April 1991. American scientists have collaborated with researchers in Denmark on a study of neuropsychological function in Danish soldiers (project HHS-5). The French are beginning an epidemiological study of their entire cohort of 25,000 Gulf War veterans. This study is starting in February 2002, and it will take two years.

2. Because the health status of Saudi Arabian soldiers has not been systematically addressed, a team of US researchers from DoD and CDC started an epidemiology study of the Saudi Arabian National Guard in 1999 (DoD-120). The objective is to examine available computerized databases for unusual health trends, comparing

soldiers who were stationed in a combat area in January 1991 (Al Khafji), with soldiers who were stationed in a non-combat area (Riyadh). Rates and causes of hospitalizations will be compared.

3. Nine projects include research objectives related to the prevalence of adverse reproductive outcomes among Gulf War veterans and their spouses. Four of these projects have been completed (HHS-4, DoD-1C, DoD-1G, VA-2A), and their results have been published. (Penman and Tarver, 1996; Cowan, et al., 1997; Araneta, et al., 1997; Araneta, et al., 2000; Kang, et al., 2001) Five of these projects have been completed, but have not published results yet (VA-2C, VA-47, DoD-1D, DoD-35, DoD-44). In addition, DoD developed an ongoing, national surveillance system, the Birth Defects Registry, in 1998. (Bush, et al., 2001; Ryan, et al., 2001)

4. Eight projects have focused on the development of simple, sensitive tests for leishmaniasis that could lead to quantification of the prevalence of infection, as well as new treatment methods. Six of these projects have been completed and have led to several publications (VA-6E, VA-16, DoD-8A, DoD-8B, DoD-9, and DoD-38). Two of these projects are ongoing (VA-15 and DoD-95).

5. The long-term mortality of Gulf War veterans will be followed by VA indefinitely (project VA-1). Four publications have focused on the causes of mortality among American Gulf War veterans, compared to non-deployed veterans. (Helmkamp, 1994; Writer, et al., 1996; Kang and Bullman, 1996; Kang and Bullman, 2001) The major finding was that there was an increased mortality rate due to external causes among Gulf War veterans, in particular, motor vehicle accidents. To date, this is the only difference in mortality rates. The British also published a mortality study of Gulf War veterans and non-deployed veterans in the UK, and they demonstrated very similar results. (Macfarlane, et al., 2000)

B. RESEARCH PRIORITIES FOR 1996

In 1995 and 1996, the number of research programs investigating Gulf War veterans' illnesses increased substantially. Many research programs began to produce results. One major development in 1996 was the information about potential exposures to chemical weapons due to the demolitions at Khamisiyah. The addition of new research, results of ongoing research, and new information about potential exposures formed the basis of a new assessment of knowledge and research. This changed the context in which the research was conducted and necessitated a revision of the 1995 *Working Plan*. The 1996 report was entitled *A Working Plan for Research on Persian Gulf Veterans' Illnesses, First Revision*. (PGVCB, 1996b) This report identified three sets of research objectives: a) shorter-term objectives; b) long-term objectives; and c) a comprehensive list of 21 research questions.

a. Short-Term Objectives

Emerging findings from ongoing research in 1995 and 1996, and new factual information on the potential for chemical weapons exposure in southern Iraq in 1991 led to the following specific, near-term recommendations for additional research:

1. More longitudinal follow-up studies of the health of Persian Gulf veterans, including those with illnesses that are difficult to diagnose.
2. Critical peer review of models used to predict exposure concentrations of environmental pollution (such as the Kuwait oil well fires) and chemical warfare agents (such as the demolition of weapons storage sites at Khamisiyah in March 1991, and aerial bombing of chemical weapons facilities during the air war).
3. Assessment of the potential for clinical investigations of the health status of the service members in the vicinity of Khamisiyah when weapons bunker 73 and the storage pit were detonated in March 1991. If deemed possible, such clinical investigations should be carried out.

Each of these research issues has been addressed since 1996, as follows:

1. Five studies include longitudinal follow-up of Gulf War veterans, in Boston, New Orleans, New Jersey, Iowa, and the United Kingdom. These studies were described in detail in Section IV.C.4. of the *Annual*

Report for 1999. (PGVCB, 2001) The scientists in Boston and New Orleans have studied their cohorts four times. The British scientists have studied their cohort three times, and the Iowa and New Jersey scientists have studied their cohorts twice. Funding was recently approved to perform longitudinal follow-up of the survey participants of the VA National Health Survey.

2. Several publications have described the results of models of the oil well fire smoke and potential releases of chemical weapons, all of which have been peer reviewed. The modeling of environmental pollution released by the Kuwaiti oil well fires has been described in detail. (Office of the Special Assistant for Gulf War Illnesses (OSAGWI), 1998b; Spektor, 1998; OSAGWI, 2000b; OSAGWI, 2000c) The results of modeling of the potential release of chemical weapons, due to the demolitions at Khamisiyah in March 1991, have been reported by two agencies. (OSAGWI, 1997; CIA, 1997; OSAGWI, 2000f) The results of modeling of the potential release of chemical weapons, due to aerial bombing of facilities during the air war, have also been published by two agencies. (CIA, 1996; OSAGWI, 2000e) Only three sites that were bombed during the air war might have released chemical weapons-Muhammadiyat, Al Muthanna, and Ukhaydir. (OSAGWI, 2001b; OSAGWI, 2001f; OSAGWI, 2001e) The results of investigations about potential exposure of US troops to the oil well fires and to chemical weapons were summarized in Appendix C. of the *Annual Report to Congress for 2000*. (MVHCB, 2001a)

3. Three funded investigations are focusing on the potential health effects among service members who were near Khamisiyah at the time of the demolitions in 1991 (DoD-1B, DoD-63, and DoD-69). One of these studies (DoD-1B) is complete and published. (Gray, et al., 1999c) In addition to these three funded projects focusing on Khamisiyah, there are three related studies that are outgrowths of other projects, which evaluate mortality rates, clinical diagnoses, and self-reported symptoms (VA-1, DoD-94, and VA-4). The mortality study is complete and published. (Kang and Bullman, 2001)

b. Long Term-Objectives

Additional research on health-related issues arising from the Gulf War experience, but with potential for more general applicability to future conflicts, was also recommended in 1996, including:

1. Investigation of the risk factors for the development of stress-related disorders including, but not limited to, post-traumatic stress disorder (PTSD).
2. Investigation of the risk factors responsible for the observed excess mortality due to external causes (e.g., motor vehicle accidents) in veterans of all wars and conflicts.
3. Exploration of the development of practical, sensitive, and specific biomarkers of exposure to chemical agents, including organophosphate nerve agents and vesicants such as sulfur mustard.
4. Toxicological and, where feasible, epidemiological research on the potential for long-term health effects resulting from low-level, sub-clinical exposures to chemical agents, particularly organophosphate agents such as sarin.
5. Development of a strategic plan for research into the potential long-term health consequences of exposure to low-levels of chemical warfare agents.

Each of these research issues has been addressed since 1996, as follows:

1. Many projects are focusing on the risk factors for the development of stress-related disorders, including post-traumatic stress disorder and major depression. Several studies that focused on stress-related disorders were published in 2001. (Ford, et al., 2001; Storzbach, et al., 2001; Erickson, et al., 2001; White, et al., 2001; Natelson, et al., 2001; Lange, et al., 2001; Schuff, et al., 2001)

2. An increased risk for mortality due to external causes has been observed in veterans of both the Vietnam War and the Gulf War. One project is evaluating the risk factors responsible for the observed increase in mortality due to motor vehicle accidents in Gulf War veterans (DoD-102). Another project evaluated the risk factors for the

significantly increased risk for unintentional injuries in Gulf War veterans (DoD-73). This resulted in an important epidemiological report in 2000. (Bell, et al., 2000)

3. Eight projects are focusing on the development of sensitive, specific biomarkers of exposure to chemical agents, including organophosphate nerve agents and vesicants such as sulfur mustard. Three of these projects have been completed (VA-6D, VA-47, DoD-49), which resulted in several publications. In 2001, five new projects were funded (DoD-135, DoD-136, DoD-137, DoD-138, DoD-146).

4. Twenty toxicological projects are focusing on the potential long-term health effects resulting from low-level, subclinical exposures to chemical agents. Thirteen of these projects are focusing on sarin. Seven epidemiological research projects are focusing on the potential long-term health effects resulting from low-level, subclinical nerve agent exposures. Six projects are focusing on possible sarin exposures due to the demolitions at Khamisiyah. (DoD-1B, DoD-63, DoD-69, DoD-94, VA-1, and VA-4) One project is evaluating the long-term effects of sarin and other nerve agents on volunteers who participated in experiments at Aberdeen Proving Grounds in the 1950s to 1970s (DoD-93).

5. A strategic research plan was developed, entitled "Effects of Low-Level Exposure to Chemical Warfare Agents: A Research Strategy." An interagency committee wrote it, including members from VA, DoD, CDC, and the Environmental Protection Agency (EPA). It was published in the *Annual Report to Congress for 1997*. (PGVCB, 1998a)

c. Comprehensive List of 21 Research Questions

In 1995, it was recommended that a contextual framework be provided for the results of completed and ongoing studies, to develop an approach for the interpretation of research results. In 1995, the Research Working Group identified 19 major research questions, to which two additional questions were added in 1996. (PGVCB, 1996b) The comprehensive Gulf War research portfolio has addressed each of these 21 questions, and relevant results have been published on each one. A comprehensive assessment of the progress made on each of these 21 questions was provided in Appendix C of the *Annual Report to Congress for 2000*. (MVHCB, 2001a)

21 Research Questions Highlighted in the 1996 *A Working Plan for Research*

1. WHAT IS THE PREVALENCE OF SYMPTOMS/ILLNESSES IN THE PERSIAN GULF VETERAN POPULATION? HOW DOES THIS PREVALENCE COMPARE TO THAT IN AN APPROPRIATE CONTROL GROUP?

2. WHAT WAS THE OVERALL EXPOSURE OF TROOPS TO LEISHMANIA TROPICA?

3. WHAT WERE THE EXPOSURE CONCENTRATIONS TO VARIOUS PETROLEUM PRODUCTS, AND THEIR COMBUSTION PRODUCTS, IN TYPICAL USAGE DURING THE PERSIAN GULF CONFLICT?

4. WHAT WAS THE EXTENT OF EXPOSURE TO SPECIFIC OCCUPATIONAL/ENVIRONMENTAL HAZARDS KNOWN TO BE COMMON IN THE PERSIAN GULF VETERANS EXPERIENCE? WAS THIS EXPOSURE DIFFERENT FROM THAT OF AN APPROPRIATE CONTROL GROUP?

5. WHAT WERE THE POTENTIAL EXPOSURES OF TROOPS TO ORGANOPHOSPHORUS NERVE AGENT AND/OR SULFUR MUSTARD AS A RESULT OF ALLIED BOMBING AT MUHAMMADIYAT AND AL MUTHANNA, OR THE DEMOLITION OF A WEAPONS BUNKER AT KHAMISIYAH?

6. WHAT WAS THE EXTENT OF EXPOSURE TO CHEMICAL AGENT, OTHER THAN AT KHAMISIYAH, IRAQ, IN THE PERSIAN GULF AS A FUNCTION OF SPACE AND TIME?

7. WHAT WAS THE PREVALENCE OF PB USE AMONG PERSIAN GULF TROOPS?

8. WHAT WAS THE PREVALENCE OF VARIOUS PSYCHOPHYSIOLOGICAL STRESSORS AMONG GULF WAR VETERANS? IS THE PREVALENCE DIFFERENT FROM THAT OF AN APPROPRIATE CONTROL POPULATION?

9. ARE PERSIAN GULF VETERANS MORE LIKELY THAN AN APPROPRIATE COMPARISON GROUP

TO EXPERIENCE NON-SPECIFIC SYMPTOMS AND SYMPTOM COMPLEXES?

10. DO PERSIAN GULF VETERANS HAVE A GREATER PREVALENCE OF ALTERED IMMUNE FUNCTION OR HOST DEFENSE WHEN COMPARED WITH AN APPROPRIATE CONTROL GROUP?

11. IS THERE A GREATER PREVALENCE OF BIRTH DEFECTS IN THE OFFSPRING OF PERSIAN GULF VETERANS THAN IN AN APPROPRIATE CONTROL POPULATION?

12. HAVE PERSIAN GULF VETERANS EXPERIENCED LOWER REPRODUCTIVE SUCCESS THAN AN APPROPRIATE CONTROL POPULATION?

13. IS THE PREVALENCE OF SEXUAL DYSFUNCTION GREATER AMONG PERSIAN GULF VETERANS THAN AMONG AN APPROPRIATE COMPARISON POPULATION?

14. DO GULF WAR VETERANS REPORT MORE PULMONARY SYMPTOMS, OR DIAGNOSES, THAN PERSONS IN APPROPRIATE CONTROL GROUPS?

15. DO GULF WAR VETERANS HAVE A SMALLER BASELINE LUNG FUNCTION IN COMPARISON TO AN APPROPRIATE CONTROL GROUP? DO GULF WAR VETERANS HAVE A GREATER DEGREE OF NON-SPECIFIC AIRWAY REACTIVITY IN COMPARISON TO AN APPROPRIATE CONTROL GROUP?

16. IS THERE A GREATER PREVALENCE OF ORGANIC NEUROPSYCHOLOGICAL AND NEUROLOGICAL DEFICITS IN PERSIAN GULF VETERANS COMPARED TO APPROPRIATE CONTROL POPULATIONS?

17. CAN SHORT-TERM, LOW-LEVEL EXPOSURES TO PYRIDOSTIGMINE BROMIDE, THE INSECT REPELLANT DEET, AND THE INSECTICIDE PERMETHRIN, ALONE OR IN COMBINATION, CAUSE SHORT-TERM AND/OR LONG-TERM NEUROLOGICAL EFFECTS?

18. DO PERSIAN GULF VETERANS HAVE A SIGNIFICANTLY HIGHER PREVALENCE OF PSYCHOLOGICAL SYMPTOMS AND/OR DIAGNOSES THAN DO MEMBERS OF AN APPROPRIATE CONTROL GROUP?

19. WHAT IS THE PREVALENCE OF LEISMANIASIS AND OTHER INFECTIOUS DISEASES IN THE GULF WAR VETERAN POPULATION?

20. DO GULF WAR VETERANS HAVE A GREATER RISK OF DEVELOPING CANCERS OF ANY TYPE WHEN COMPARED WITH AN APPROPRIATE CONTROL POPULATION?

21. ARE GULF WAR VETERANS EXPERIENCING A HIGHER MORTALITY RATE THAN THAT OF AN APPROPRIATE CONTROL POPULATION? ARE SPECIFIC CAUSES OF DEATH RELATED TO SERVICE IN THE PERSIAN GULF REGION?

C. RESEARCH PRIORITIES FOR 1998

In 1998, the RWG reevaluated the issue of research priorities. (PGVCB, 1999a) Key factors that guided the RWG in it discussions were recent research findings, the current breadth and depth of the research portfolio in key areas, and the availability of resources to develop needed new initiatives.

1. Research on Treatments for Gulf War Veterans' Illnesses

Some Gulf War veterans with unexplained illnesses are suffering from symptoms such as fatigue, musculoskeletal pain, and cognitive problems. These symptom complexes significantly overlap with other symptom complexes identified in the civilian population such as chronic fatigue syndrome (CFS) and fibromyalgia (FM). As with illnesses in Gulf War veterans, no clearly defined etiologic agent has been identified for CFS and FM.

The RWG determined that experimental treatment methods that have been applied to persons with CFS or FM deserved further exploration in the context of Gulf War veterans' illnesses. Consequently, the RWG established the development of treatment protocols for unexplained illnesses as a research priority. In 1999, VA and DoD jointly began two major multi-site treatment trials. These were the Exercise Behavioral Therapy Trial (VA-62 and DoD-115) and the Antibiotic Treatment Trial (VA-55 and DoD-119). Details of these two trials were provided in Section IV.C.1. of the *Annual Report for 1999*. (PGVCB, 2001) Total investment by VA and DoD for these two trials was more than $9.6 million and $5.6 million,

respectively. These treatment trials have been completed and will be published in 2002.

Also, VA has funded an Institute of Medicine study to identify effective treatments for health problems in Gulf War veterans. This study started in 1999, and it was published in July 2001. (IOM, 2001) It is described in Section IV.B. of this *Annual Report*.

2. Longitudinal Follow-Up for Gulf War Veterans' Illnesses

The RWG has concluded that research approaches to determine the long-term health of veterans are a high priority. Several research projects funded by the Federal Government have longitudinal components built into them. These projects are directed toward understanding the progress of Gulf War veterans' illnesses over time. In 2001, there are five studies that include longitudinal follow-up, in Boston, New Orleans, East Orange, New Jersey, Iowa, and the United Kingdom. These studies were described in detail in Section IV.C.4. of the *Annual Report for 1999*. (PGVCB, 2001) Preliminary results of these follow-up studies were published in the *Proceedings of the 2001 Conference on Illnesses among Gulf War Veterans: A Decade of Scientific Research*. (MVHCB, 2001b)

3. Disease Prevention

The substantial proportion of veterans who have reported ill health following deployment to the Gulf War represents a significant level of morbidity that might be preventable. To ensure that future health problems in future deployments can be prevented, the RWG has endorsed future research aimed generally at disease prevention, and more specifically at prevention of stress-related symptoms and conditions. This is consistent with the recommendations of a number of oversight committees. The Federal investment focusing on the pathophysiology of stress-related illnesses has markedly increased, and now there are more than 90 projects with a primary or secondary focus on Brain and Nervous System Function. This investment in improved understanding of the pathophysiology of stress-related illnesses should lead to better methods of disease prevention and treatment.

4. Improved Hazard Assessment

The Presidential Review Directive-5 (PRD-5) recognized that the ability to better anticipate environmental and occupational hazards prior to deployments could potentially reduce morbidity associated with unintended or unanticipated exposures. (NSTC, 1998) The RWG, in conjunction with the Working Groups that developed the PRD-5, recommended enhanced research efforts aimed at improving methods of hazard identification and risk assessment for environmental and occupational hazards. Such research efforts should emphasize the reality of complex multiple exposures to more than one hazardous agent.

In 1998, the DoD established new funding for programmed research. The purpose of this program element funding, explicitly put into DoD's budget requests, was to address issues of Gulf War veterans' illnesses, which may also be of concern in future deployments. The funding is approximately $20 million per year for fiscal years 1999 to 2002, and about $10 million per year thereafter. The overall objective is to enhance force health protection in future deployments. The program is guided by a tri-service DoD panel and is coordinated with the RWG. Specific research areas in 1999 to 2001 have included:

1. prevention and treatment of persistent stress symptoms;
2. methods to assess health hazards from toxic chemicals and mixtures and to monitor exposures;
3. improved safety assessments of medical materiel, including potential interactions in operational environments; and
4. epidemiological studies to continue long-term follow-up of Gulf War veterans and to improve health status monitoring in future deployments.

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